## REMARKS

Claims 1, 3, 4, and 6 – 10 are pending.

Claims 1 and 4 are rejected under 35 USC 112, first paragraph, because the specification is not enabling for using aminoglcoside antibiotics to treat diseases other than glaucoma that are caused by premature stop mutations in a gene. In response, Applicant has amended Claims 1 and 4 to recite open-angle glaucoma. Support for this amendment can be found in the Specification at, for example, page 1. line 28 – page 2, line 10, and page 4, line 13 – 21.

Claims 1, 2, 4, 5, 7, and 8 are rejected under 35 U.S.C. 102(a) as being anticipated by Miller et al. (Journal of the American Animal Hospital Association, 2000, Vol. 36 No. 5, pages 431 – 438) in light of Alward et al. (New England Journal of Medicine, 1998, Vol. 338 No. 15, pages 1022-1027). According to the Examiner, Miller discloses methods of using a topical eye drop composition comprising gentamicin to treat glaucoma in dogs. The Examiner cites Alward et al. for its disclosure that "glaucoma is associated with stop mutations in the GLC1A gene. Additionally, the Examiner rejected Claims 1 – 10 under 35 U.S.C. 103(a) as unpatentable over Miller et al. and Barton-Davis et al. in light of Alward et al. on the same basis as the Section 102 rejection and assertions that it would be obvious for one skilled in the art to optimize the concentration of antibiotic and that the determination of the specific etiology of the glaucoma (i.e., the specific mutation) would necessarily be part of any treatment regiment.

Applicant respectfully traverses the rejections of Claims 1, 2, 4, 7, and 8 under §102(a) and Claims 1 – 10 under §103(a). Miller et al. compared the ability of a beta blocker drug, betaxolol, to a combination of demecarium bromide and a topical corticosteroid in their ability to prevent glaucoma in the fellow eye of dogs with unilateral, primary closed angle glaucoma. The corticosteroid happened to itself be a combination product of gentamicin and betamethasone. There is no indication that the gentamicin was important or played any role in the study.

There is a very well-recognized distinction between closed-angle glaucoma and open-angle glaucoma. One skilled in the art would expect the use of a corticosteroid – in this case a combination of gentamicin and betamethasone – in the treatment of closed-angle glaucoma. Indeed, the Miller et al. reference indicates that corticosteroids are one of the three types of

drugs commonly used to treat closed-angle glaucoma in dogs (See Miller et al, page 431, last line of the first paragraph of the Introduction). In contrast, however, one skilled in the art would not use a corticosteroid to treat open-angle glaucoma because corticosteroid therapy is known to exacerbate the elevated IOP of glaucoma patients (i.e. almost all open-angle glaucoma patients are "corticosteroid responders"). See Clark, et al., "Steroid-Induced Glaucoma," Glaucoma Science and Practice, 2003, Chapter 18 (pp. 197 -206); and Clark, "Steroids, Ocular Hypertension, and Glaucoma," *Journal of Glaucoma*, 4(5):354-369, 1995. Copies of these two references are attached to this paper for the convenience of the Examiner. Thus, one skilled in the art would not be motivated to use the "corticosteroid" (gentamicin/betamethasone combination) of Miller et al. in the treatment of open-angle glaucoma. Moreover, there is no indication or suggestion in either the Miller et al. or the Alward et al. references that a premature stop mutation is associated with closed-angle glaucoma. One skilled in the art willing to ignore the fact that corticosteroids should not be used to treat open-angle glaucoma would have no reasonable belief that such corticosteroids (or antibiotic/corticosteroid combinations) would effectively treat open-angle glaucoma caused by a stop mutation in an open-angle glaucoma gene.

Applicant believes that the above amendments and remarks have placed Claims 1, 3, 4, and 6 – 10 in condition for allowance. Accordingly, allowance of the claim in this application is respectfully requested.

Respectfully submitted,
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7/6/06
Date

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# Glaucoma

## Science and Practice

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# Steroid-Induced Glaucoma

Abbot F. Clark, Ph.D., and John C. Morrison, M.D.

Although relatively rare, steroid-induced glaucoma presents several connections with primary open-angle glaucoma (POAG). These include a stronger tendency to develop steroid response in the families of patients with POAG, and recent discoveries of tantalizing connections between the glaucoma gene, *MYOC* (*GLC1A*, *TIGR*), and its glucocorticoid induction in the trabecular meshwork (TM). Alterations in TM cell function, morphology, extracellular matrix production, and the cytoskeleton also occur in both of these conditions. These similarities suggest that steroid-induced glaucoma may provide important insights into the genetics and cellular mechanisms of POAG.

Clinically, steroid-induced glaucoma is characterized by highly elevated intraocular pressure (IOP) and is always associated with glucocorticoid administration. The eyes are quiet, and the angle appears normal by gonioscopy. Pressure elevation generally correlates with the steroid dose and is most common with topical and periocular administration, although it can also follow systemic, and even inhaled, steroid use. Because these eyes are generally asymptomatic, diagnosis relies on appropriate recognition and monitoring of patients at risk. Failure to recognize and control elevated pressure can result in characteristic glaucomatous optic nerve damage and irreversible visual field loss.

This glaucoma is best treated by withdrawal of the steroid preparation, and standard topical glaucoma management, as needed. However, elevated IOP can persist in some cases, suggesting either conversion or an underlying predisposition to develop POAG. Persistent glaucoma requires chronic medical management, and occasionally, laser treatment or standard filtration surgery.

## Background

The discovery of glucocorticoids was a major breakthrough in the treatment of inflammatory and autoimmune diseases, both systemic and ocular. However, their widespread use has uncovered many serious side effects, including ocular hypertension and iatrogenic glaucoma. First reported by McLean, Stern, and Francois[1-3] in association with systemic administration of glucocorticoids, this secondary glaucoma is clinically similar to POAG and can cause similar irreversible visual field changes. Numerous reports, summarized in several detailed reviews,[4-7] followed this initial discovery, documenting the development of steroid-induced ocular hypertension and secondary glaucoma with various glucocorticoids and routes of administration.

In the early 1960s, Armaly[8] and Becker[9] independently studied the effect of the potent glucocorticoids dexamethasone and betamethasone on IOP. Topical application of 0.1% formulations three to four times a day for 4 to 6 weeks produced three levels of response in the normal population: (1) 4 to 6% of individuals, termed "high responders," developed pressures above 31 mm Hg, or increases greater than 15 mm Hg above baseline; (2) one third of the population were "moderate responders," with pressures between 20 and 31 mm Hg, or pressure rises of 6 to 15 mm Hg; and (3) the remainder were "nonresponders," with IOPs less than 20 mm Hg and pressure increases less than 6 mm Hg.

When retested for steroid response, the nonresponder and moderate responder groups showed some variablity in the magnitude of IOP elevation. However, greater than 98% of those individuals initially catagorized as high responders remained either high or moderate responders.[10] Although initial reports suggested that steroid responsiveness was inherited in a simple Mendelian manner,[9] results of twin studies and the variable reproducibility of the steroid response have challenged this view.[10,11] However, there still remains a strong link between steroid-induced ocular hypertension and POAG.[6,7]

Administration of topical ocular glucocorticoids to patients with POAG produces a moderate to high response in nearly all subjects,[12,13] and descendents of

POAG patients demonstrate a higher rate of steroid response than the general population.[14,15] Finally, both prospective and retrospective clinical studies indicate that normal individuals classified as high steroid responders are more likely to develop POAG.[16,17] These findings have led some to suggest that testing for steroid responsiveness may identify patients at risk for developing POAG. However, this has not become routine practice because of variability in the extent of the response[10] and the perceived potential risk to normal individuals.

Among other groups of patients, both diabetics[18] and high myopes[19] also have higher rates of steroid responsiveness compared with the general adult population. Studies in children are conflicting. Whereas one study of Israeli children reported lower rates of steroid responsiveness,[20] rates in Japanese[21] and Chinese[22] children may be higher.

In addition to the responder status of the patient, the development of steroid-induced ocular hypertension also depends on the potency, duration, and dose of the steroid; its route of administration; and its ability to enter the eye.[6] In general, those agents with the greatest anti-inflammatory efficacy and the highest affinity for the glucocorticoid receptor are most likely to induce ocular hypertension. Routes most apt to induce ocular hypertension are topical ocular administration as well as intraocular or periocular injections. The steriod response can also develop after receiving systemic glucocorticoids, or glucocorticoids applied to the skin, intranasally, or by inhalation.[4,6]

**PEARL...** The development of steroid-induced ocular hypertension depends on family history and on the potency, duration, and dose of the steroid, its route of administration, and its ability to enter the eye.

Topical ocular steroids can also generate ocular hypertension in rabbits,[23,24] cats,[25,26] and monkeys.[26,27] In monkeys, approximately 40% of otherwise normal animals develop increased IOP. This response is both reversible and reproducible.[28]

## PATHOPHYSIOLOGY

Steroids cause a number of cellular, biochemical, and molecular changes in the TM.[7] One or more of these changes, many of which resemble those of POAG, could produce increased resistance to aqueous humor outflow, elevated IOP, and, eventually, glaucomatous optic nerve damage (Table 18–1).

Human eyes with steroid-induced glaucoma have increased deposition of extracellular material in the trabecular beams, as well as fingerprint-like deposits in the uveal meshwork and fibrillar deposits in the juxtacanalicular tissue of the TM (Fig. 18–1A–D).[29–31] Tissue culture experiments using isolated, human anterior segments in a perfusion chamber show that glucocorticoids can have

**TABLE 18–1** EFFECTS OF GLUCOCORTICOIDS ON THE TRABECULAR MESHWORK

| | |
|---|---|
| TM Cell Function | Inhibition of proliferation and migration[41,43]<br>Inhibition of phagocytosis[43,44]<br>IOP elevation and decreased hydraulic conductivity*[31,46] |
| TM cell morphology | "Activation" of TM cells (increased endoplasmic reticulum, Golgi complexes, and secretory vesicles)*[29,33]<br>Increased TM cell size and nucleus size[33]<br>Increased capacity for biosynthesis[33] |
| TM extracellular matrix (ECM) | Increased deposition of ECM material in TM*[29–31]<br>Increased expression of fibronectin,* laminin, collagen, and elastin[34–37]<br>Decreased expression of t-PA and MMPs[7,39–40]<br>Altered expression of glycosaminoglycans (decreased hyaluronic acid and increased chondroitin sulfate)*[7,38]<br>Thickening of trabecular beams*[29–31] |
| TM cytoskeleton | Formation of cross-linked actin networks*[33,41]<br>Increased expression of select actin-binding proteins<br>Generation of microtubule tangles[33]<br>Increased resistance to cytoskeletal disruption |
| TM cell junctional complexes | Altered gap-junction morphology<br>Altered expression of the tight junction protein ZO-1[46]<br>Altered expression of select integrins[35–36] |
| TM cell gene expression | Increased expression of the glaucoma gene *MYOC* (*TIGR*)*[7,48,49,53]<br>Increased expression of select ECM molecules[34–37]<br>Decreased expression of MMPs[7,39–40] |

*Indicates alterations observed in primary open-angle glaucoma. TM, trabecular meshwork; IOP, intraocular pressure; t-PA, tissue plasminogen activator; TIGR, trabecular meshwork induced glucocorticoid response; MMP, matrix metalloproteinase.

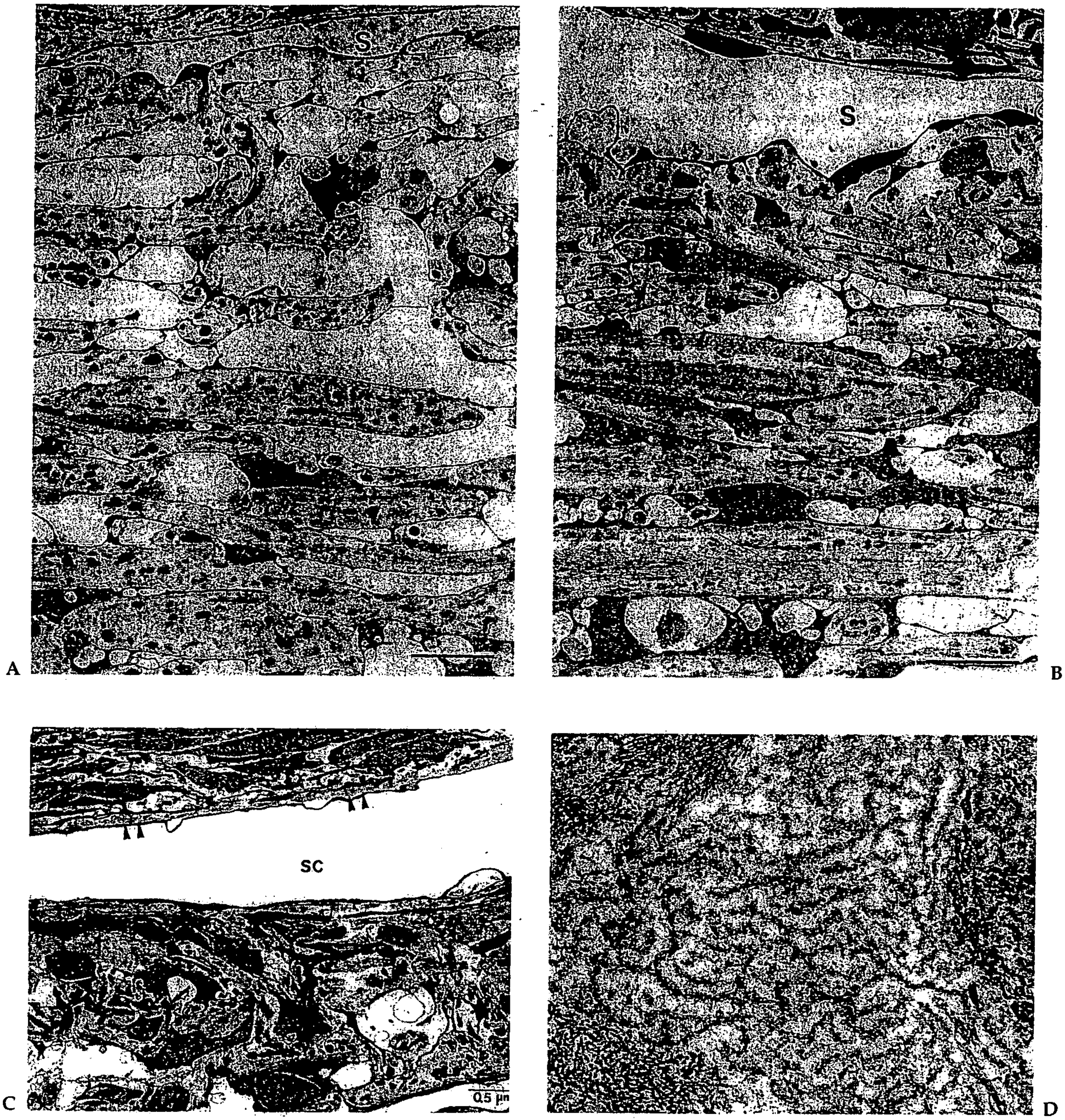



**FIGURE 18-1** Morphological effects of glucocorticoids on trabecular meshwork tissue. (A) Transmission electron microscopy of the outflow pathway of a normal perfusion-cultured human eye. (B) The outflow pathway of a perfusion-cultured human eye with DEX-induced ocular hypertension, showing accumulation of fine fibrillar material (asterisk) and cellular debris (arrows). (C) The trabecular meshwork (juxtacanalicular tissues and canal of Schlemm) of a 60-year-old patient with steroid-induced glaucoma from systemic prednisolone administration. Fine fibrillar extracellular material (star) appears within the juxtacanalicular tissue and is increased adjacent to the outer wall endothelium (arrowheads). (D) Higher magnification of fingerprint-like extracellular material in the trabecular meshwork of a 13-year-old patient with glaucoma induced by topical ocular steroids. SC, Schlemm's canal. [(A) and (B) were reproduced with permission from Clark AF, Wilson K, deKater AW, Allingham RR, McCartney MD. Dexamethasone-induced ocular hypertension in perfusion cultured human eyes. *Invest Ophthalmol Vis Sci* 1995;36:478–489. (C) and (D) courtesy of Douglas Johnson, M.D., and reproduced with permission from Johnson D, Gottanka J, Flugel C, Hoffman F, Futa T, Lutjen-Drecoll E. Ultrastructural changes in the trabecular meshwork of human eyes treated with glucocorticoids. *Arch Ophthalmol* 1997;115:373–383.]

direct effects on the TM.[31] Thirty percent of such eyes develop ocular hypertension, similar to the steroid response rate in the normal human population. This elevated IOP is associated with increased deposition of extracellular matrix molecules, which has also been reported in the outflow pathway of patients with POAG.[32]

**SPECIAL CONSIDERATION**

Corticosteroids produce several alterations in the TM that also occur in POAG. These include "activation" of TM cells, increased deposition of extracellular matrix material, alterations of the trabecular cell cytoskeleton, and increased expression of the glaucoma gene, myocilin.

Steroids can cause a number of cellular and biochemical changes in the TM, and the challenge is to determine which of these produce ocular hypertension and steroid-induced glaucoma. Steroids can directly affect the morphology of TM cells. This includes increasing nuclear and cell size and increasing the endoplasmic reticulum, Golgi complex, and secretory vesicles, all of which suggest activation of TM cells and an increase in their protein biosynthetic capacity.[33]

Several biochemical studies in TM cells now support these morphologic findings, showing that steroid treatment increases the production of extracellular matrix (ECM) proteins,[34–37] and alters expression of glycosaminoglycans.[7,38] In addition, glucocorticoids may further encourage the deposition of ECM molecules in the meshwork by suppressing the expression of extracellular proteinases,[7,39,40] which normally help turn over the ECM.

Steroids can produce a dramatic reorganization of the TM cell cytoskeleton.[33,41] In glucocorticoid-treated TM cells, the actin microfilament network, normally organized into bundles of filaments, become rearranged into geodesic dome-like structures, known as cross-linked actin networks (CLANs) (Fig. 18–2A,B). The time-course for the formation and reversibility of CLANs closely correlates with that for the induction of glucocorticoid-mediated ocular hypertension.[41] CLANs also appear to occur in TM cells isolated from donors with POAG.[42]

Steroid-induced alterations in the TM cytoskeleton may lead to decreased proliferation,[41,43] migration,[41] and phagocytosis[43,44] of TM cells. Reduced proliferation and migration likely produce the diminished cellularity seen in the TM of patients with steroid-induced glaucoma. Because these cells are normally highly phagocytic and provide a "self-cleaning filter" function to the TM, inhibition of phagocytosis may lead to progressive accumulation of extracellular debris, a "clogging" of the meshwork, and increased aqueous outflow resistance.[45]

Steroids can also alter gap junctions (protein complexes that couple TM cells together) and mediate cell-to-cell communication. In addition, steroids may tighten connections between cells and increase aqueous outflow resistance.[46] Glucocorticoids also can change the expression of several TM cell integrins,[35,36] which are ECM receptors found in the cell membrane linked to the actin cytoskeleton, further affecting TM cell function and migration.

The recent discovery of the first glaucoma gene[47] presents another potential connection between POAG and steroid-induced glaucoma. This gene, variously named *GLC1A*,[47] *TIGR* (trabecular meshwork induced glucocorticoid response),[48,49] and *MYOC* (the current, preferred name),[50] is a glucocorticoid-induced gene expressed in the TM. Initially discovered as the gene responsible for the autosomal dominantly inherited form of juvenile glaucoma, the myocilin gene is involved in a small, approximately 4%, subset of adult onset POAG.[51,52] Specific mutations of this gene correlate with the development of a more severe, juvenile-onset type of glaucoma, whereas other mutations appear to cause milder, later-onset disease.[52] Increased myocilin expression has also been reported in the TM of patients with several different types of glaucoma.[53]

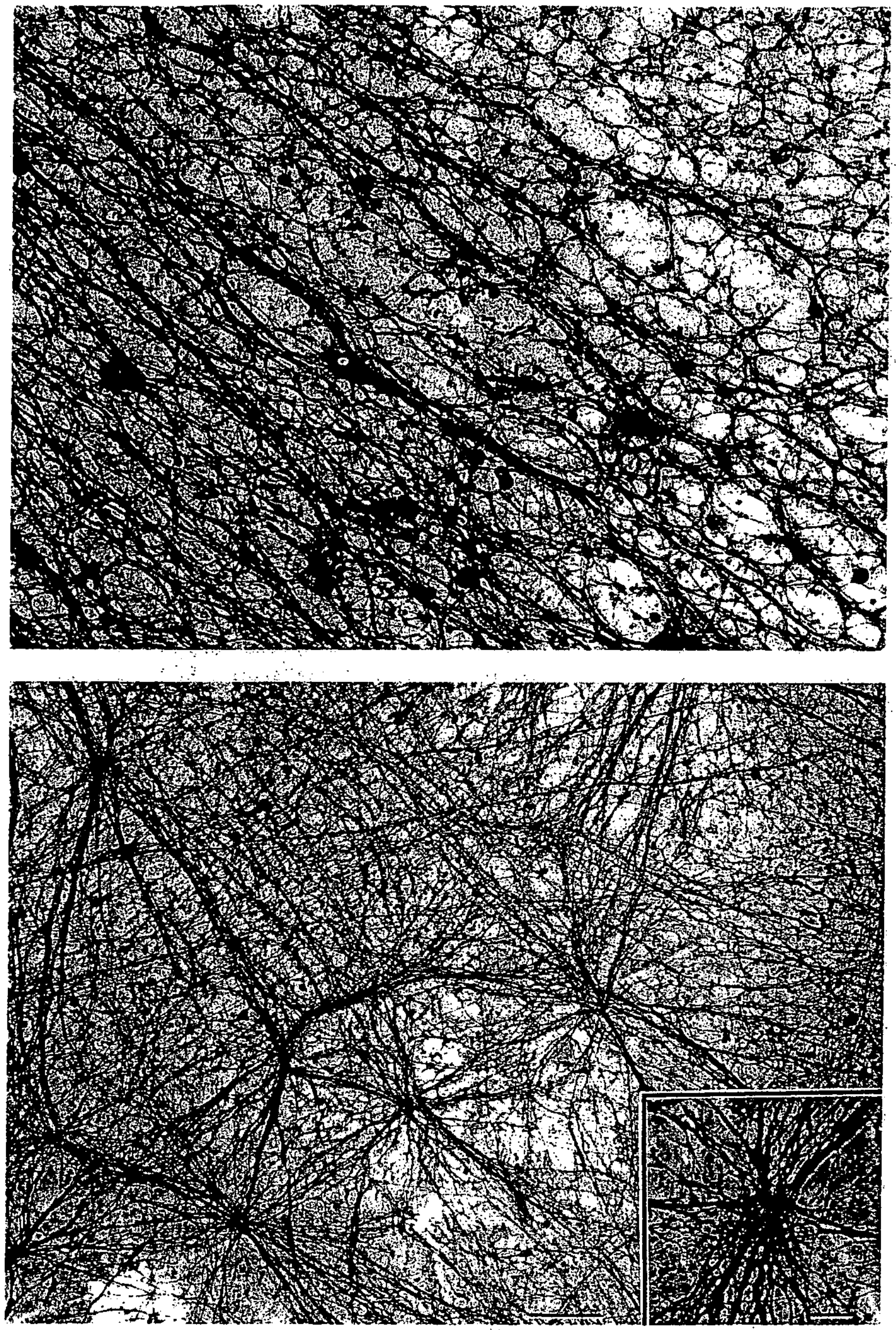
Myocilin (TIGR) initially was characterized as a protein induced by glucocorticoids in cultured TM cells (Fig. 18-3).[43] Although its function is currently unknown, myocilin appears in both intracellular and extracellular forms and is expressed in many ocular and nonocular tissues. Myocilin has also been found in cells of the optic nerve head,[54] where it may play a role in glaucomatous optic nerve damage.

Recent work has shown that glaucomatous mutations in *MYOC* prevent myocilin from being secreted from TM cells.[53a] In addition, mice[53b] and humans[53c] lacking both copies of the *MYOC* gene do not appear to develop glaucoma. These data suggest that glaucomatous mutations in *MYOC* cause a gain of function phenotype, possibly due to an inadequate ability of the TM to handle misfolded mutant myocilin, leading to defective TM cell function.

Some investigators suggest that myocilin is responsible for glucocorticoid-induced ocular hypertension[43,48,49] and speculate that excessive production of myocilin leads to increased aqueous outflow resistance. Although the time-course and dose-response characteristics of myocilin induction in cultured TM cells closely mimic the induction of glucocorticoid-induced ocular hypertension, it is not known if myocilin is responsible for, or merely associated with, the steroid response. Genetic studies have not revealed any mutations in the coding region of the myocilin gene to account for this response.[28,55]

**CONTROVERSY**

There are no definitive data that differentiate whether myocilin is responsible for, or merely associated with, glucocorticoid-induced ocular hypertension.



A

B

**FIGURE 18-2** Effect of glucocorticoids on trabecular meshwork cell cytoskeleton. (A) Transmission electron microscopy (TEM) evaluation of normal TM cell showing actin microfilament bundles forming linear arrays of stress fibers. (B) TEM showing DEX-induced reorganization of microfilaments into geodesic dome-like structures called cross-linked actin networks (CLANs). [Reprinted with permission from Clark AF, Wilson K, McCartney MD, Miggans ST, Kunkle M, Howe W. Glucocorticoid-induced formation of cross-linked actin networks in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 1994;35:281–294.]

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Patients with steroid-induced glaucoma have relatively few symptoms (Table 18–2). The IOP rise is generally gradual and painless, although rare patients experience a typical brow ache. Decreased visual acuity usually results from associated subcapsular cataract, the underlying condition that necessitated steroid treatment or, rarely, from end-stage optic nerve damage.

Eyes with steroid-induced glaucoma are quiet, with clear corneas (unless bedewed from elevated pressure) and open, normal-appearing anterior chamber angles. It normally takes at least several days, and usually weeks, to develop ocular hypertension from steroid treatment,

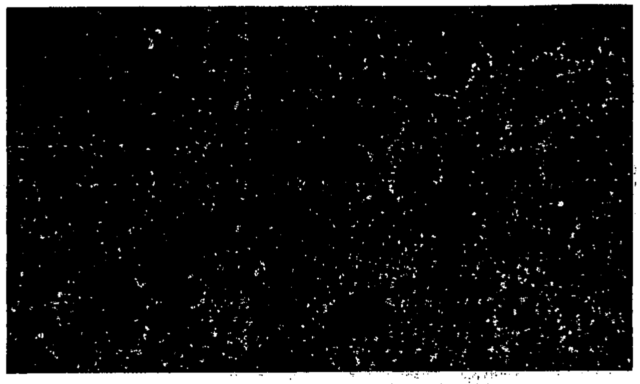


**FIGURE 18–3** Expression of the glaucoma gene *MYOC* in cultured human trabecular meshwork (TM) cells treated with dexamethasone for 2 weeks. Myocilin is found intracellularly as discrete particles (stained red-yellow) surrounding the nucleus. Actin microfilaments are stained green. In many of the TM cells, myocilin is found inside "cages" of cross-linked actin networks (CLANs).

**TABLE 18–2** DIAGNOSIS OF GLUCOCORTICOID-INDUCED GLAUCOMA

| | |
|---|---|
| History | History of steroid use (any route)<br>Family history of glaucoma or steroid-induced glaucoma |
| Symptoms | Generally few<br>Decreased vision secondary to corneal edema, end-stage visual field loss, steroid-induced cataract or the underlying condition |
| Signs | Occasional epithelial edema from IOP<br>Open angle, normal appearance<br>Elevated IOP, may be marked<br>IOP elevation generally resolves following discontinuation of corticosteroids<br>Typical glaucomatous optic nerve damage and visual field loss |

IOP, intraocular pressure.

and the IOP usually remains elevated, often in the 30 to 60 mm Hg range, for as long as the patient receives the agent. Although steroid-induced ocular hypertension is generally reversible, several reports document continued IOP elevation, even long after withdrawal of the steroid.[56–58] This may depend in part on the dosage and duration of treatment because eyes with longer treatment are more likely to demonstrate a sustained pressure rise.

The optic nerve damage from steroid-induced glaucoma appears typical for all glaucomas, ranging from generalized cupping to vertical elongation of the optic cup and focal notching, erosion, and undermining of the disc margin (Fig. 18–4A–C). Visual field loss appears similarly characteristic. Although the steroid-induced IOP elevation is reversible in most cases, damage to the optic nerve and visual field is not.

The major differential diagnosis of steroid-induced glaucoma is POAG (Table 18–3). The history of steroid use can be key to making this differentiation. Because many people do not include topical skin preparations when responding to the general query regarding what medicines they take, they must be specifically questioned about topical as well as ocular and systemic medications. If the patient does use topical corticosteroids, determining the strength of preparation, the site of application, and the frequency is important because the extent of pressure rise can be proportional to the dose received by the eye. As stated earlier, patients with a family history of glaucoma are more likely to develop a steroid response, as well as POAG.

The clinical course may also help make the diagnosis, which may only be evident after the suspected offending agents are discontinued. Onset of IOP elevation generally occurs after days to weeks of administration, although acute increases (within hours) have been reported in POAG patients.[59] In general, IOP returns to normal following discontinuation of glucocorticoids.

Because IOP may not revert to normal, it may not be possible to determine if these patients represent true, irreversible steroid-induced glaucoma or latent cases of POAG that either developed coincidentally with the steroid use, or were unmasked by these drugs. Because IOP elevation is often variable, a rechallenge with the offending agent may be the only way to confirm the diagnosis.

In general, ciliary flush, cells, and flare in the anterior chamber and, in advanced cases, anterior and posterior synechiae, will distinguish uveitic glaucoma from steroid-induced glaucoma.

However, confusion may arise when treating active uveitis with intense topical corticosteroids. In this situation, IOP may initially be low from the inflammation itself, but will then increase due to suppression of the inflammation and recovery of aqueous humor production. This can result in a significant pressure rise, which may be interpreted as a steroid response. However, the relative rarity of steroid-induced glaucoma, coupled with the need for aggressive management of ocular inflammation, argues in favor of treating the uveitis until it is substantially resolved. The steroid dosage can then be reduced, changed to a less potent corticosteroid, or discontinued in favor of a "steroid-sparing" agent. Some cases require standard glaucoma therapy to allow time to treat the inflammation properly and wean the patient off the corticosteroids.

**PITFALL...** Steroid treatment of acute uveitis can suppress inflammation and allow the recovery of aqueous humor production. The resulting increase in IOP may be mistaken for steroid-induced glaucoma.

Other, less common, forms of uveitis may also present diagnostic confusion, such as glaucomatocyclytic crisis, or Posner-Schlossman syndrome. This condition, dis-


A


B

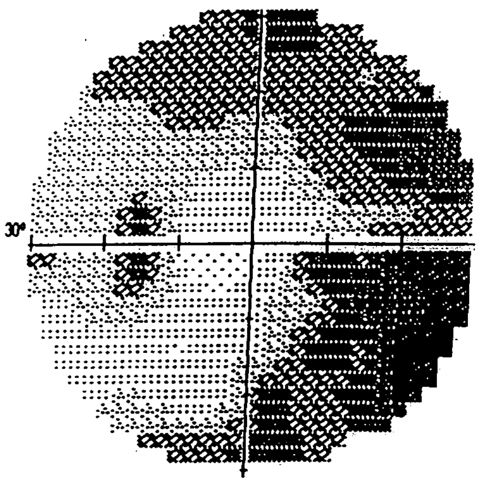

C

**FIGURE 18–4** A patient with severe atopic dermatitis who applied triamcinolone cream to the skin of his eyelids daily for several months, especially the left. Pressure OS at times was as high as 58 mm Hg. The left optic disc shows rapid progression of cupping from (A) May 1990 to (B) April 1991, and was accompanied by (C) glaucomatous visual field loss. Intraocular pressure at the time of the photograph in (B) was 12 mm Hg.

cussed more fully in Chapter 26, often lacks the traditional signs of uveitis, with the exception of mild anterior chamber reaction, discrete keratic precipitates, and the remarkable elevation in IOP. Treatment with corticosteroids typically helps control the inflammation and, secondarily, the glaucoma.

Steroid-induced glaucoma may paradoxically resemble low-tension glaucoma if it produces optic nerve damage, which is then detected after the patient has discontinued the corticosteroids and the pressure has returned to normal (Fig. 18–4A–C). Again, the history of steroid use is crucial to making the correct diagnosis.

**TABLE 18–3** DIFFERENTIAL DIAGNOSIS OF STEROID-INDUCED GLAUCOMA

| *Condition* | *Differentiating Features* |
|---|---|
| Primary open-angle glaucoma | No steroid use<br>May be difficult to differentiate in cases that do not resolve after discontinuing corticosteroids |
| Uveitic glaucoma | Anterior chamber cells, flare<br>Keratic precipitates, synechiae<br>Treatment of uveitis with corticosteroids may produce elevated IOP due to recovery of ciliary body function, and may be mistaken for a steroid response<br>Therapeutic dilemma arises from need to treat ocular inflammation with corticosteroids, both of which may elevate IOP |
| Glaucomatocyclytic crisis | Subtle anterior chamber reaction<br>IOP elevation episodes independent of steroid use |
| Normal-tension glaucoma | Glaucomatous optic nerve damage with normal IOP may resemble steroid-induced glaucoma following discontinuation of steroids and normalization of IOP<br>Lack of history of corticosteroid use |
| Juvenile glaucoma | Anterior iris insertion with flat contour<br>Patient age |

IOP, intraocular pressure.

Juvenile glaucoma may occasionally also be confused with steroid-induced glaucoma. The IOP rise may be marked, with an open angle and quiet anterior chamber. Subtle signs, such as anterior insertion of the iris and a flat iris plane, generally help with this differentiation (see Chapter 17).

## MANAGEMENT

Prevention remains the most effective treatment for steroid-induced glaucoma (Table 18–4). This involves using these potent medications only when indicated and limiting dosages to those necessary to achieve the desired effect. However, necessary corticosteroids should never be withheld out of concern for creating steroid-induced glaucoma.

When corticosteroid treatment is necessary, particularly with potent topical ocular agents and periocular injections, the physician should always monitor the patient for steroid-induced glaucoma. This includes obtaining baseline IOP measurements, mostly to rule out pre-existing glaucoma. Pressure monitoring should initially occur every 4 to 6 weeks, decreasing to once every several months after an initial response has been ruled out. Typically, if steroids are prescribed for an ocular problem, the examinations necessary to monitor the ocular condition, with IOP measurements incorporated at every opportunity, are sufficient to monitor the patient for steroid-induced glaucoma.

**SPECIAL CONSIDERATION**

Discontinuing corticosteroids can be complicated by the need to treat the underlying condition, the unpredictable rate at which the glaucoma resolves, and the fact that the glaucoma can persist long after the steroids are stopped.

**TABLE 18–4** MANAGEMENT OF STEROID-INDUCED GLAUCOMA

| | |
|---|---|
| Prevention | Avoid unnecessary or prolonged use of corticosteroids, particularly in patients with a family history of glaucoma<br>Recognize the use of steroids by any route<br>Recognize the relative tendency of different steroid preparations to cause glaucoma |
| Treatment | Carefully monitor patients on corticosteroids, especially those with a family history of glaucoma<br>Discontinue steroids (if possible)<br>Use alternative, "steroid-sparing" medications<br>Suspect POAG if IOP remains elevated after discontinuing corticosteroids<br>Standard medical, laser, and surgical management to prevent glaucomatous optic nerve damage |

IOP, intraocular pressure; POAG, primary open-angle glaucoma.

Although discontinuing steroid treatment may offer the most logical management for steroid-induced glaucoma, this is often not possible. Under these circumstances, the steroids must simply be continued, often at an aggressive pace (such as with uveitis), to get the inflammation under control as rapidly as possible. Consultation with physicians responsible for any systemic steroid administration is also necessary, at least to alert them to the problem and request that they taper and discontinue steroids as rapidly as possible. In the meantime, the glaucoma itself must be treated medically, at least temporarily, to protect the optic nerve.

Discontinuing steroids can also present other problems. Although stopping topical medications is relatively simple, the rate at which the glaucoma resolves is unpredictable, and there is no consensus as to how long to wait before deciding that removing steroids has not resolved the situation. If the glaucoma results from a periocular corticosteroid injection, surgical excision of the steroid can be done, but usually involves removing associated scar tissue, Tenon's capsule, and fat.

Unfortunately, stopping corticosteroids does not always resolve the glaucoma. This circumstance may arise simply because the glaucoma has resulted as a complication of the underlying condition, such as uveitis, leaving permanent functional trabecular damage. Alternatively, the steroid may "unmask" a patient's latent POAG that then simply persists.

Medical management of steroid-induced glaucoma is usually undertaken to protect the optic nerve, particularly if it is already severely damaged. The extremely high elevation of IOP seen in many of these cases may also necessitate treatment even if the optic nerve appears healthy.

Medical treatment is usually a temporizing measure until steroids can be safely discontinued. This includes the entire array of available topical antiglaucoma medications, beginning with aqueous humor suppressants. These include adrenergic antagonists, followed by either alpha agonists or topical carbonic anhydrase inhibitors.

Latanoprost in this condition specifically has not been thoroughly evaluated. However, this, as well as miotics, may be effective, particularly as additive agents. Although long-term complications with either of these agents are generally not a concern in this self-limited condition, both may be contraindicated in patients with uveitis or trauma.

The efficacy of argon laser trabeculoplasty (ALT) in this condition may be slightly less than in other forms of open-angle glaucoma. However, it is particularly attractive when considered as a means of avoiding filtration surgery, particularly if corticosteroids can be discontinued and the need for chronic treatment is limited.

Surgical management consists primarily of filtration surgery, and its success is essentially the same as for other open-angle glaucomas. This option should be reserved for those cases in which medications and laser have failed to control the pressure, and in which resolution through discontinuation of the corticosteroids is not anticipated to occur soon enough to protect the optic nerve.

## REFERENCES


1. McLean JM. Discussion of Woods AC: Clinical and experimental observation on the use of ACTH and cortisone in ocular inflammatory disease. *Trans Am Ophthalmol Soc* 1950;48:293.
2. Stern JJ. Acute glaucoma during cortisone therapy. *Am J Ophthalmol* 1953:36:389.
3. Francois J. Cortisone et tension oculaire. *Ann Oculist* 1954;187:805–816.
4. Skuta GL, Morgan RK. Corticosteroid-induced glaucoma. In: Ritch R, Shields MD, Krupin T, eds. *The Glaucomas.* St. Louis: CV Mosby; 1996:1177–1188.
5. Urban RC, Dreyer EB. Corticosteroid-induced glaucoma. *Int Ophthalmol Clin* 1993;33:135–139.
6. Clark AF. Steroids, ocular hypertension, and glaucoma. *J Glaucoma* 1995;4:354–369.
7. Wordinger RJ, Clark AF. Effects of glucocorticoids on the trabecular meshwork: towards a better understanding of glaucoma. *Prog Retinal Eye Res* 1999;18: 629–667.
8. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. *Invest Ophthalmol* 1965;4:187–197.
9. Becker B. Intraocular pressure response to topical corticosteroids. *Invest Ophthalmol* 1965;4:198–205.
10. Palmberg PF, Mandell A, Wilensky JT, Podos SM, Becker B. The reproducibility of the intraocular pressure response to dexamethasone. *Am J Ophthalmol* 1975;80:844–856.
11. Schwartz JT, Reuling FH, Feinleib M, Garrison RJ, Collie DJ. Twin study on ocular pressure following topically applied dexamethasone. *Arch Ophthalmol* 1973;90:281–286.
12. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics, II: the effect of dexamethasone in the glaucomatous eye. *Arch Ophthalmol* 1963;70:492–499.
13. Becker B, Hahn KA. Topical corticosteroids and heredity in primary open-angle glaucoma. *Am J Ophthalmol* 1964;57:543–551.
14. Becker B, Chevrette L. Topical corticosteroid testing in glaucoma siblings. *Arch Ophthalmol* 1966;76: 484–487.
15. Bartlett JD, Woolley TW, Adams CM. Identification of high ocular pressure responders to topical ophthalmic corticosteroids. *J Ocular Pharm* 1993;9:35–45.
16. Kitazawa Y, Horie T. The prognosis of corticosteroid-responsive individuals. *Arch Ophthalmol* 1981;99: 819–823.
17. Lewis JM, Priddy T, Judd J, et al. Intraocular pressure response to topical dexamethasone as a predictor for the development of primary open-angle glaucoma. *Am J Ophthalmol* 1988;106:607–612.
18. Becker B. Diabetes mellitus and primary open-angle glaucoma: the XXVII Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1971;77:1–16.
19. Podos SM, Becker B, Morton WR. High myopia and primary open-angle glaucoma. *Am J Ophthalmol* 1966;62:1039–1043.
20. Biedner BZ, David R, Grudsky A, Sachs U. Intraocular pressure response to corticosteroids in children. *Br J Ophthalmol* 1980;64:430–431.
21. Ohji M, Kinoshita S, Ohmi E, Kuwayama Y. Marked intraocular pressure response to instillation of corticosteroids in children. *Am J Ophthalmol* 1991;112:450–454.
22. Kwok AKH, Lam DSC, Ng JSK, Fan DSP, Chew S-J, Tso MOM. Ocular hypertensive response to topical steroids in children. *Ophthalmology* 1997;104: 2112–2116.
23. Knepper PA, Collins JA, Frederick R. Effect of dexamethasone, progesterone, and testosterone on IOP and GAGs in the rabbit eye. *Invest Ophthalmol Vis Sci* 1985;26:1093–1100.
24. Ticho U, Lahav M, Berkowitz S, Yofee P. Ocular changes in rabbits with corticosteroid-induced ocular hypertension. *Br J Ophthalmol* 1979;63:646–650.
25. Zhan G-L, Miranda OC, Bito LZ. Steroid glaucoma: corticosteroid-induced ocular hypertension in cats. *Exp Eye Res* 1992;54:211–218.
26. Bhattacherjee P, Paterson CA, Spellman JM, Graff G, Yanni JM. Pharmaological validation of a feline model of steroid-induced ocular hypertension. *Arch Ophthalmol* 1999;117:361–364.
27. DeSantis L, Garthwaite C, Knepper PA. Dexamethasone induction of ocular hypertension in the primate [ARVO abstract]. *Invest Ophthalmol Vis Sci* 1990;31:488.
28. Fingert JH, Clark AF, Craig JE, et al. Evaluation of the myocilin (MYOC) glaucoma gene in monkey and human steroid-induced ocular hypertension. *Invest Ophthalmol Vis Sci* 2001;42:145–152.
29. Rohen JW, Linner E, Witmer R. Electron microscopic studies on the trabecular meshwork in two cases of corticosteroid-glaucoma. *Exp Eye Res* 1973;17:19–31.
30. Johnson D, Gottanka J, Flugel C, Hoffman F, Fluta T, Lutjen-Drecoll E. Ultrastructural changes in the trabecular meshwork of human eyes treated with glucocorticoids. *Arch Ophthalmol* 1997;115:373–383.
31. Clark AF, Wilson K, deKater AW, Allingham RR, McCartney MD. Dexamethasone-induced ocular hypertension in perfusion cultured human eyes. Invest *Ophthalmol Vis Sci* 1995;36:478–489.
32. Babizhayev MA, Brodskaya MW. Fibronectin detection drainage in outflow system of human eyes in ageing and progression of open-angle glaucoma. *Mech Ageing Dev* 1989;47:145–157.
33. Wilson K, McCartney MD, Miggans ST, Clark AF. Dexamethasone induced ultrastructural changes in cultured human trabecular meshwork cells. *Current Eye Res* 1993;12:783–793.
34. Steely HT, Browder SL, Julian MB, Miggans ST, Wilson KL, Clark AF. The effects of dexamethasone on fibronectin expression in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 1992;33: 2242–2250.

35. Dickerson JE, Steely HT, English-Wright SL, Clark AF. The effect of dexamethasone on integrin and laminin expression in cultured human trabecular meshwork cells. *Exp Eye Res* 1998;66:731–738.
36. Zhou L, Li Y, Yue BY. Glucocorticoid effects on extracellular matrix proteins and integrins in bovine trabecular meshwork cells in relation to glaucoma. *Int J Mol Med* 1998;1:339–346.
37. Yun AJ, Murphy CG, Polansky JR, Newsome DA, Alvarado JA. Proteins secreted by human trabecular meshwork cells: glucocorticoid and other effects. *Invest Ophthalmol Vis Sci* 1989;30:2012–2022.
38. Engelbrecht-Schuner S, Sieger A, Prehm P, Lutjen-Drecoll E. Dexamethasone treatment decreases hyaluronan-formation by primate trabecular meshwork cells in vitro. *Exp Eye Res* 1997;64:539–543.
39. Snyder RW, Stamer WD, Kramer TR, Seftor REB. Corticosteroid treatment and trabecular meshwork proteases in cell and organ culture supernatants. *Exp Eye Res* 1993;57:461–468.
40. Samples JR, Alexander JP, Acott TS. Regulation of the levels of human trabecular matrix metalloproteinases and inhibitor by interleukin-1 and dexamethasone. *Invest Ophthalmol Vis Sci* 1993;34:3386–3395.
41. Clark AF, Wilson K, McCartney MD, Miggans ST, Kunkle M, Howe W. Glucocorticoid-induced formation of cross-linked actin networks in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 1994;35:281–294.
42. Clark AF, Miggans ST, Wilson K, McCartney MD. Cytoskeletal changes in cultured human glaucoma trabecular meshwork cells. *J Glaucoma* 1995;4:183–188.
43. Polansky JR, Kurtz RM, Fauss DJ, Kim RY, Bloom E. In vitro correlates of glucocorticoid (GC) induced glaucoma model in human trabecular meshwork (HTM) cells. In: Krieglstein GK, ed. *Glaucoma Update IV*. Berlin: Springer-Verlag; 1991:20–29.
44. Matsumoto Y, Johnson DH. Dexamethasone decreases phagocytosis by human trabecular meshwork in situ. *Invest Ophthalmol Vis Sci* 1997;38:1902–1907.
45. Bill A. The drainage of aqueous humor. *Invest Ophthalmol Vis Sci* 1975;14:1–3.
46. Underwood JL, Murphy CG, Chen J, et al. Glucocorticoids regulate transendothelial fluid flow resistance and formation of intracellular junctions. *Am J Physiol* 1999;277:C330–C342.
47. Stone EM, Fingert JH, Alward WLM, et al. Identification of a gene that causes primary open-angle glaucoma. *Science* 1997;275:668–670.
48. Polansky JR, Fauss DJ, Chen P, et al. Cellular pharmacology and molecular biology of the trabecular meshwork inducible glucocorticoid response gene product. *Ophthalmologica* 1997;211:126–139.
49. Nguyen TD, Chen P, Huang WD, Chen H, Johnson DH, Polansky JR. Gene structure and properties of TIGR, an olfactomedin-related glycoprotein cloned from glucocorticoid-induced trabecular meshwork cells. *J Biol Chem* 1998;273:6341–6350.
50. Kubota R, Noda S, Wang Y, et al. A novel, myosin-like protein (myocilin) expressed in the connecting cilium of the photoreceptor: molecular cloning, tissue expression, and chromosomal mapping. *Genomics* 1997;41:360–369.
51. Fingert JH, Heon E, Liebman JM, et al. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. *Hum Mol Genet* 1999;8:899–905.
52. Alward WLM, Fingert JH, Johnson AT, et al. Clinical features associated with mutations in the chromosome 1 open-angle glaucoma gene (GLC1A). *N Engl J Med* 1998;338:1022–1027.
53. Lutjen-Drecoll E, May CA, Polansky JR, Johnson DH, Bloementhal H, Nguyen TD. Localization of the stress proteins aB-crystallin and trabecular meshwork inducible glucocorticoid response protein in normal and glaucomatous trabecular meshwork. *Invest Ophthalmol Vis Sci* 1998;39:517–525.
53a. Jacobson N, Andrews M, Shepard AR, et al. Non-secretion of mutant proteins of the glaucoma gene myocilin in cultured trabecular meshwork cells and in aqueous humor. *Hum Mol Genet* 2001;10:117–125.
53b. Kim BS, Savinova OV, Reedy MV, et al. Targeted disruption of the myocilin gene (MYOC) suggests that human glaucoma-causing mutations are gain of function. *Mol Cell Biol* 2001;21:7707–7713.
53c. Lam DS, Leung YF, Chua JK, et al. Truncation mutations in the TIGF gene in individuals with and without primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 2000;41:1386:1391.
54. Clark AF, Kawase K, English-Wright S, et al. Expression of the glaucoma gene myocilin (MYOC) in the human optic nerve head. *FASE B J* 2001;15:1251–1253.
55. Craig JE, Snibson GR, Alward WLM, et al. Exclusion of GLC1A coding region mutations as a common cause of steroid-induced ocular hypertension [ARVO abstract]. *Invest Ophthalmol Vis Sci* 1998;39:S687.
56. Weinreb RN, Polansky JR, Kramer SG, Baxter JD. Acute effects of dexamethasone on intraocular pressure in glaucoma. *Invest Ophthalmol Vis Sci* 1985;26:170–175.
57. Francois J. Corticosteroid glaucoma. *Ann Ophthalmol* 1977;9:1075.
58. Espildora J, Vicuna P, Diaz E. Cortison-induced glaucoma: a report on 44 affected eyes. *J Fr Ophthalmol* 1981;4:503.
59. Spaeth GL, Rodrigues MM, Weinreb SP. Steroid-induced glaucoma: a persistent elevation of intraocular pressure, B: histopathologic aspects. *Trans Am Ophthalmol Soc* 1977;75:353.
60. Ferry AP, Harris WP, Nelson MH. Histopathologic features of subconjunctivally injected corticosteroids. *Am J Ophthalmol* 1987;103:716.

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Basic Sciences in Clinical Glaucoma

# Steroids, Ocular Hypertension, and Glaucoma

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Summary: Glucocorticoids (GC) can regulate aqueous humor outflow and have often been associated with primary open angle glaucoma (POAG). The ocular or systemic administration of glucocorticoids can cause the elevation of intraocular pressure by increasing aqueous humor outflow resistance via morphological and biochemical changes in the trabecular meshwork (TM). The ability of glucocorticoids to induce ocular hypertension is dependent on individual responsiveness, the potency of the glucocorticoid, the route of administration, and the duration of treatment. Glucocorticoid-induced ocular hypertension occurs not only in humans, but also in rabbits, cats, dogs, and nonhuman primates. Glucocorticoids have a multitude of effects on trabecular meshwork cells causing changes in TM protein expression, cytoskeletal organization, extracellular matrix deposition, cell shape, and cell function. Many of these changes in the TM may be responsible for the generation of glucocorticoid-induced ocular hypertension. There have been several reports of increased cortisol levels, altered cortisol metabolism, and differential glucocorticoid responsiveness in patients with ocular hypertension and POAG. However, there is as yet no clear evidence for a causal role between glucocorticoids and primary open angle glaucoma. Finally, there is evidence that a variety of steroids of differing pharmacological steroid classes can lower the elevated intraocular pressure (IOP) in glucocorticoid-induced ocular hypertension and/or in glaucoma patients. Continued research in the coming years should (a) identify the molecular mechanisms responsible for glucocorticoid-induced ocular hypertension and glaucoma, (b) determine whether glucocorticoids play a role in the pathogenesis of primary open angle glaucoma, and (c) determine the therapeutic utility of anti-glaucoma steroids. Key Words: Glucocorticoids—Steroids—Ocular hypertension—Trabecular meshwork.

Steroids are a physiologically and pharmacologically important class of hormones and drugs. A number of endogenous steroid hormones, including cortisol (or corticosterone in rodents), aldosterone, testosterone, and estradiol, have been found in the eye (1,2), and a variety of ocular tissues have been shown to contain steroid receptors (3–7). However, it appears that glucocorticoids are the most important steroid hormones in the eye. Glucocorticoids are generally responsible for the regulation of carbohydrate, lipid, and protein metabolism. In addition, exogenously administered glucocorticoids are unequaled in their therapeutic efficacy as antiinflammatory and immunosuppressive agents (8), and are extensively used to treat a variety of ocular diseases and conditions (9,10).

Early research suggested that glucocorticoids could also be used to treat glaucoma. However, it was soon discovered that glucocorticoid adminis-

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tration could lead to the development of ocular hypertension and iatrogenic glaucoma (11–17). There has subsequently been a great deal of research on the role of glucocorticoids in ocular hypertension and glaucoma, portions of which have been previously reviewed, including the clinical aspects of corticosteroid-induced glaucoma (18–20), the ocular antiinflammatory aspects of glucocorticoids (9), and the side effects of ocular glucocorticoid therapy (21). In addition, a recent, brief review on corticosteroid glaucoma has been published (22). The purpose of the present review article is to provide a brief overview of steroids and glaucoma with emphasis on (a) glucocorticoid-induced ocular hypertension in humans and animals, (b) the association of glucocorticoids with glaucoma, (c) the effects of glucocorticoids on the trabecular meshwork, and (d) steroids that lower IOP.

## GLUCOCORTICOID-INDUCED OCULAR HYPERTENSION IN HUMANS

### Steroid Responsiveness

Corticosteroids were discovered to be potent antiinflammatory agents in the 1940s (23) and were soon utilized to treat ocular inflammation (24,25). The initial reports that topical ocular cortisone treatment (12,14), as well as systemic corticosteroid treatment (11,13,15), could lead to the development of ocular hypertension and iatrogenic glaucoma have been confirmed by a number of investigators (26–30). Armaly (27) and Becker (28) independently showed that the normal population could be divided into three categories based on responsiveness to topical ocular administration of a potent glucocorticoid (i.e., betamethasone or dexamethasone). Four to six percent of the population were classified as high responders, developing steroid-induced pressure rises of >15 mm Hg or IOPs of >31 mm Hg following glucocorticoid administration three to four times a day for 4–6 weeks. Approximately one-third of the population were moderate responders, developing pressure rises of 6–15 mm Hg or IOPs of 20 and 31 mm Hg. The rest of the population were considered nonresponders with pressure rises of <6 mm Hg and IOPs of <20 mm Hg. Both Armaly (30) and Becker (28) suggested that the ocular hypertensive response to topical glucocorticoid administration could be inherited in a simple Mendelian fashion. This view has been challenged based on results of other studies, including differing steroid responsiveness in twins (31) and the lack of absolute reproducibility of the test to determine steroid responsiveness (32). Although there may be some variability in IOP response in the nonresponder and moderate responders upon rechallenge to topical glucocorticoid administration, 98% of patients initially identified as high responders continue to be high to moderate responders upon rechallenge (32). As noted by Urban and Dreyer (22), only a few individuals in the twin study were identified as high responders. Therefore, the twin study could not conclusively demonstrate or disprove the possible genetic inheritance of steroid responsiveness.

In contrast to the normal population, certain other groups tend to have a higher ocular hypertension response rate when given topical glucocorticoids. It has been reported that almost all primary open angle glaucoma (POAG) patients are moderate to high steroid responders (33,34), although this view is not universally accepted (35). Steroid-induced ocular hypertension has even been reported in glaucoma patients after trabeculectomy (36) and Molteno implantation (37). In addition to steroid responsiveness in glaucoma patients, a number of studies have shown that close relatives of POAG patients also have an elevated rate of steroid responsiveness compared to the general population (38–41). Diabetics (42), high myopes (43), and patients with certain rheumatic diseases (44) have also shown higher rates of steroid responsiveness.

There are conflicting reports on the risk of young children to the development of glucocorticoid-induced glaucoma. A study of 44 young Israeli patients (mean age, 10 years) undergoing 6 weeks of topical 0.1% dexamethasone therapy for vernal conjuctivitis indicated a low rate of ocular hypertension (i.e., 11% with IOP rises of >6 mm Hg) (45). In contrast, a study of 11 Japanese children averaging 5.5 years old who received topical ocular 0.1% dexamethasone after strabismus surgery showed that nine of these children had significant IOP increases within 1–2 weeks (46). The IOP elevation did not appear to be due to postsurgical trauma, as treatment of a second group of children with a less potent glucocorticoid (0.1% FML) did not lead to the development of ocular hypertension in any of the patients. It is difficult to generalize from these studies; apparently, differences in a child's age, the therapeutic indication, and/or the child's ethnic background (e.g., Israeli vs. Japanese) determines steroid responsiveness.

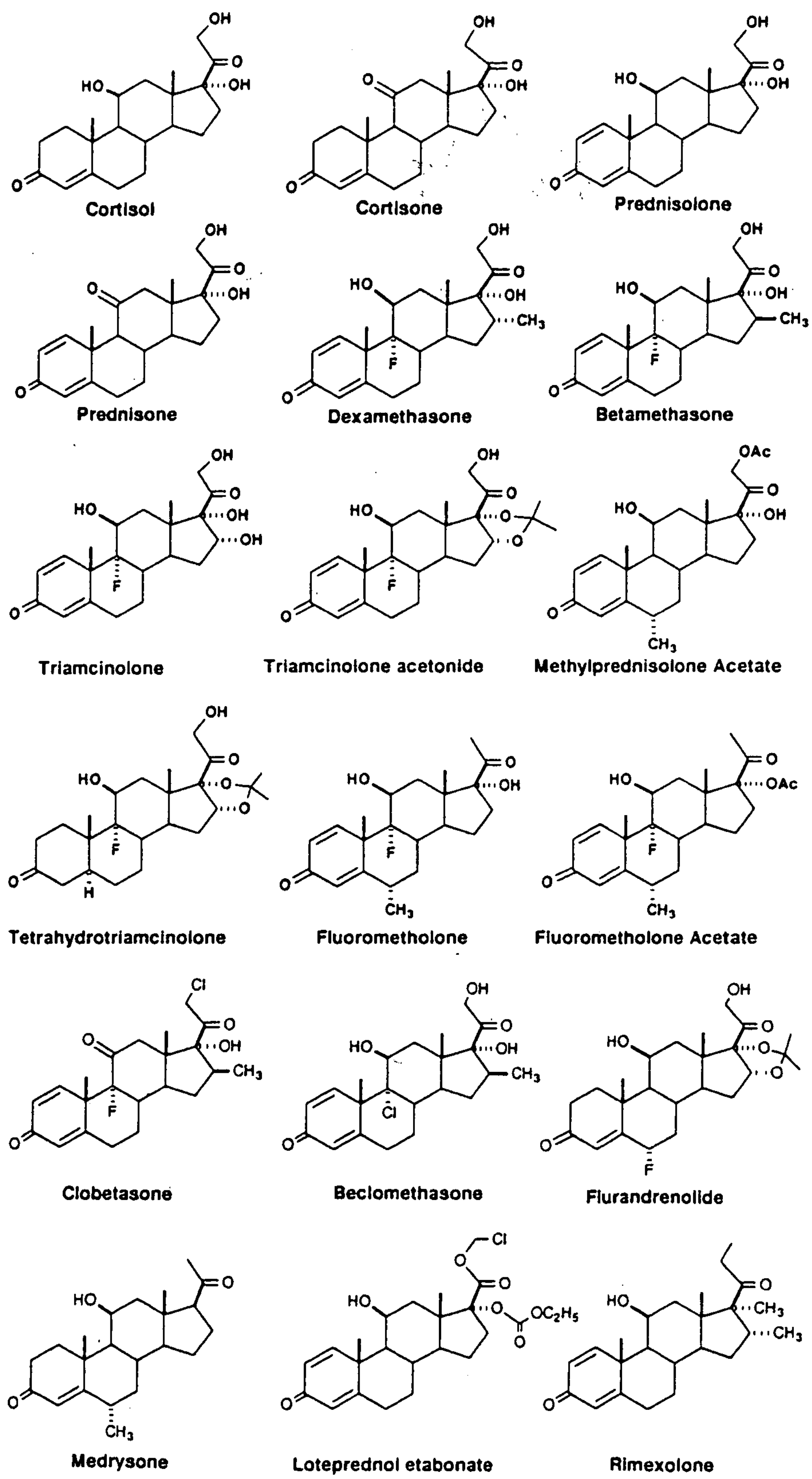


**FIG. 1.** Structures of glucocorticoids reported to have effects on intraocular pressure. These steroids have varying propensities to induce ocular hypertension in humans (see text for details).

## Antiinflammatory Steroids and IOP

A variety of glucocorticoids have been shown to increase intraocular pressure in humans (Fig. 1). Factors determining the degree of glucocorticoid-induced ocular hypertension include the GC dose and potency, ocular bioavailability and metabolism, route of administration, and duration of treatment. The majority of topical ocular glucocorticoids appear to have relatively favorable rates of corneal penetration. The ability of certain glucocorticoids to induce ocular hypertension in steroid responders is dose dependent (47,48). In general, the propensity of certain glucocorticoids to generate ocular hypertension closely matches their antiinflammatory potency (47–50). For example, the synthetic glucocorticoids dexamethasone (DEX) and betamethasone are potent antiinflammatory agents and also have the greatest propensity to raise IOP (47–54). Various forms of dexamethasone, including the free alcohol, 21-phosphate, and 21-acetate, are all effective at inducing IOP rises (47,49–51,54). The cornea, as well as other tissues in the anterior chamber, have the capacity to metabolize DEX-phosphate and DEX-acetate to the parent free alcohol (55). Prednisolone, prednisolone phosphate, and prednisolone acetate are also relatively potent antiinflammatory agents that can induce significant ocular hypertension (49,53,56,57). Glucocorticoids with intermediate antiinflammatory activity such as fluorometholone (FML) (48–50,52, 58), clobetasone butyrate (53,57), hydrocortisone (cortisol) (47,49), and tetrahydrotriamcinolone (47–49), are capable of generating ocular hypertension in steroid responders and glaucoma patients, but to a lesser degree than the more potent glucocorticoids such as dexamethasone and betamethasone. Although FML appears to be a potent glucocorticoid in vitro (49), its lower antiinflammatory and ocular hypertensive activity in vivo may be due to ocular metabolism and subsequent inactivation (9,21) as well as its relatively poor rate of ocular penetration (59). The relatively weak antiinflammatory agent medrysone (49) has little propensity to induce ocular hypertension (47–50,60), although a significant pressure increase with medrysone administration has been reported in one patient (60).

Loteprednol etabonate, FML acetate, and rimexolone are new topical ocular antiinflammatory steroids undergoing extensive clinical evaluation. Loteprednol etabonate was designed as a "soft metabolizable" glucocorticoid that would have antiinflammatory activity at the site of application and be inactivated systemically. Some metabolic inactivation occurs in the eye (61), which may be responsible for the reported lower propensity of loteprednol etabonate to raise IOP in steroid responders (56). FML acetate appears to be a more potent ocular antiinflammatory agent than FML (62), perhaps due to its greater ocular penetration (21). A clinical study in steroid responders has shown that topical administration of 0.1% FML acetate is less apt to raise IOP than 0.1% DEX (54). Rimexolone has been reported to be an effective antiinflammatory agent comparable to prednisolone acetate, but with a more limited potential to raise IOP (63).

## Clinical Aspects

Glucocorticoid-induced ocular hypertension due to the topical ocular administration of a potent glucocorticoid is generally progressive over the course of weeks or months. It is not unusual to get dramatic intraocular pressure increases (e.g., IOPs 40–50 mm Hg) after 4–6 weeks of topical ocular administration with a potent glucocorticoid such as dexamethasone or betamethasone in steroid responders. In general, the ocular hypertension is reversible upon withdrawal of the glucocorticoid treatment (16,17), although cases of irreversible IOP elevation have been reported (35,64). The duration of topical glucocorticoid treatment may be one factor in determining the reversibility of the glucocorticoid-induced ocular hypertension (65).

Glucocorticoid-induced glaucoma (GIG) is an iatrogenic secondary form of open angle glaucoma. Its clinical characteristics are very similar to POAG with elevated pressure, a normal-appearing anterior chamber angle by gonioscopic examination, glaucomatous damage to the optic nerve, and characteristic visual field loss (18–20). GIG is generally differentiated from POAG by careful analysis of the patient's medication history. It is possible for a patient who has previously been treated with glucocorticoids to present with clinical features of normal tension glaucoma, because the ocular hypertensive phase is often reversible upon discontinuation of the glucocorticoid therapy, but the damage to the optic nerve persists (66). GIG in infants may mimic congenital glaucoma with the development of buphthalmia and edematous corneas (67).

Glucocorticoids have been shown to induce ocular hypertension when administered by a variety of

ocular routes, including topical ocular drops, topical ointments (68,69), periocular injections (70,71), as well as by systemic routes of administration (11, 13,15,29). The administration of intraocular repository glucocorticoids can lead to dangerous elevations of IOP even in patients who are resistant to topical ocular steroid-induced ocular hypertension (71). There have been several recent reports of steroid-induced ocular hypertension and glaucoma in patients using inhaled glucocorticoids (72,73). In patients who receive glucocorticoids by two routes of administration (e.g., topical ocular as well as systemic), the propensity to develop ocular hypertension may be additive (74). The IOP response to systemic glucocorticoid administration appears to require longer treatment times and to involve a lower percentage of patients than topical ocular steroid administration (19,20,74). There have been several reports of ocular hypertension in patients with Cushing's syndrome who have elevated levels of the endogenous glucocorticoid cortisol (75,76). Pressures returned to normal when the patients were surgically treated to remove the source of excess cortisol production.

### Aqueous Dynamics

There have been a variety of studies on the effects of glucocorticoids on aqueous humor dynamics, and it is generally considered that glucocorticoids exert their effects on IOP by increasing aqueous humor outflow resistance without dramatically affecting the rate of aqueous humor formation. Both topical ocular (16,17,39) as well as systemic (15) glucocorticoid administration can decrease the aqueous outflow facility to glaucomatous levels. This steroid-induced ocular hypertension has also been associated with marked changes in the trabecular meshwork. Trabeculectomy samples from GIG patients have shown significant morphological changes in the trabecular meshwork including the marked deposition of fibrillar and amorphous extracellular material in the cribriform region and in adjacent trabecular beams, densification of the cribriform region, occlusion of the aqueous outflow channels, and "activation" of some of the remaining trabecular cells (77–80).

Glucocorticoids may also have an acute effect (within hours) on intraocular pressure in addition to their more chronic effect on the aqueous humor outflow facility. Endogenous glucocorticoid levels are correlated with the diurnal variation in IOP seen in both animals and humans (81,82), although a recent study appears to have ruled out a causal role for glucocorticoids in this regulation in humans (83). Glaucoma patients given oral dexamethasone have been reported to develop acute increases in IOP within hours of the glucocorticoid administration (84). The mechanism(s) responsible for this acute steroid-induced ocular hypertension is currently unknown.

## ANIMAL MODELS OF GLUCOCORTICOID-INDUCED OCULAR HYPERTENSION

In addition to humans, several other animal species have been shown to develop ocular hypertension when treated with glucocorticoids. Rabbits treated topically or by subconjunctival injections of the potent glucocorticoid dexamethasone generate a 5–10 mm Hg rise in IOP over the course of 2–6 weeks of treatment (85–91). Younger rabbits appear to be more susceptible to the development of steroid-induced ocular hypertension (89). The steroid-induced pressure elevation is due to a decrease in the aqueous humor outflow facility (85) and is associated with morphological changes in the trabecular meshwork consisting of increased deposition of glycosaminoglycans (GAGs), amorphous ground substance and collagen fibrils, as well as activation of trabecular cells (87,88). Changes in the biochemical composition of the trabecular meshwork GAGs involving decreases in hyaluronate and increased deposition of chondroitin sulfate occurred in the eyes of dexamethasone-induced ocular hypertensive rabbits (89,90). In the majority of studies, the development of rabbit glucocorticoid-induced hypertension occurred progressively over the course of 2–6 weeks. However, there has been one report of acute rises in IOP in rabbits after only 1–2 days of topical ocular dexamethasone treatment (91). The rabbit may not be an ideal model in which to study glucocorticoid-induced ocular hypertension. Rabbits appear to become resistant to the ocular hypertensive effects of glucocorticoids when treated for periods greater than 6–8 weeks (86). In addition, they are very sensitive to glucocorticoids so that topical ocular glucocorticoid treatment often causes significant systemic side effects including loss in body weight, adrenal atrophy, excessive glycogen deposition in the liver, and sometimes death of the animal.

Glucocorticoid-induced ocular hypertension has also been reported in three other species. Adult cats developed significant ocular hypertension after 2–3

weeks of topical ocular dexamethasone administration (92,93). This ocular hypertension was the result of a decreased aqueous outflow facility which was most likely due to increased extracellular matrix deposition in the outflow channels (93). Unlike rabbits treated topically with glucocorticoids, there did not appear to be significant systemic effects (i.e., loss in body weight) in these cats. Adult dogs treated topically with dexamethasone over the course of several months have also been reported to develop ocular hypertension (94).

One group has reported that topical ocular or subconjunctival administration of potent glucocorticoids to rhesus, pigtail, and cynomolgus monkeys for several months failed to produce ocular hypertension (95). In contrast, weekly subTenon's injections of a slow release form of dexamethasone (DEX-acetate) in young Macaque monkeys generated ocular hypertension (>5 mm Hg rise in pressure) in ~40% of the treated animals over the course of 4–8 weeks (96). In addition, preliminary data (Chandler M, McLaughlin M, and Clark AF, 1995, unpublished observations) suggest that topical ocular administration of 0.1% dexamethasone tid for 4 weeks induced significant IOP elevation (+10 mm Hg) in five out of 11 cynomolgous monkeys, and this ocular hypertension was reversible after discontinuation of DEX administration. There was no apparent ocular or systemic toxicity evident in any of these studies. The discrepancy between these studies may be due to methodological differences. In the first study which reported a lack of steroid responsiveness, the monkeys were untreated or the right eye treated with topical ocular 0.1% DEX (tid) or subconjunctival injections of methylprednisolone acetate every 2 weeks for 3 months (95). The outflow facility of the steroid-treated and untreated monkeys was determined by the constant pressure servoperfusion technique, and there were no apparent differences in the frequency distribution of outflow facilities between treated and untreated eyes. In the latter two studies, which demonstrated steroid responsiveness, the monkeys were treated bilaterally by weekly subTenon's injections of DEX-acetate for several months (96) or by topical ocular administration of 0.1% DEX (tid) for 4 weeks (Chandler M, McLaughlin M, Clark AF, 1995, unpublished observations), and IOPs were measured by applanation pneumotonometry both before and during treatment.

It therefore appears that, in addition to humans, ocular glucocorticoid administration can induce ocular hypertension, decrease aqueous humor outflow, and biochemically as well as morphologically alter the trabecular in a variety of animals.

## ASSOCIATION OF GLUCOCORTICOIDS WITH PRIMARY OPEN ANGLE GLAUCOMA

Over the past 30 years, a number of investigators have suggested that glucocorticoids may be involved in the pathogenesis of primary open angle glaucoma. Although there is no clear evidence for a direct involvement of steroids in glaucoma, there are a number of studies implicating their association with this disease.

As discussed earlier, topical ocular administration of a potent glucocorticoid can lead to the generation of significant elevations in intraocular pressure in 4–6% of the general population. These subjects are referred to as "steroid responders." In a prospective study, Kitazawa and Horie (97) followed a group of steroid responders for at least 10 years and found that the steroid responders were more likely to eventually develop POAG compared to those subjects who were determined to be nonresponders. Lewis et al. (98) retrospectively examined a large group of steroid responders and reported that these patients also had a higher risk of developing POAG compared to age-matched nonresponders. Both of these studies as well as studies demonstrating increased steroid responsiveness in close relatives of POAG patients (38–41) suggest that steroid responsiveness may be an important risk factor in the development of POAG.

A number of groups have independently reported that POAG patients have elevated levels of the endogenous glucocorticoid, cortisol, in their blood compared to age-matched subjects without POAG (99–102) as well as increased levels of a noncortisol glucocorticoid in the plasma of POAG patients (103). One group has also found higher levels of cortisol in the aqueous humor of POAG patients than in nonglaucomatous patients undergoing cataract extraction (100). One of the difficulties in interpreting these studies is the significant natural diurnal fluctuation in blood cortisol levels in which plasma cortisol levels can vary by as much as 10-fold (104). Plasma cortisol levels can also significantly change depending on the nutritional (feeding/fasting times) and stress status of the subjects. Several early studies (105,106) have suggested that

stress is a risk factor for the development of POAG, which may implicate stress hormones, such as cortisol, as being associated with the disease.

It has also been suggested that POAG is primarily a systemic defect in the pituitary-hypothalamus-adrenal axis. This suggestion is based on studies of increased sensitivity of POAG patients and IOP steroid-responders to plasma cortisol suppression after systemic challenge with oral dexamethasone (107,108). However, it does not appear that the cortisol suppression test is a useful predictor of the development of POAG. In a prospective study of high IOP responders to topical glucocorticoids, there was no difference in the plasma cortisol responsiveness to oral dexamethasone administration between those individuals who developed glaucomatous visual field changes and those who did not (109). The increased sensitivity of cultured, mitogen-stimulated peripheral blood lymphocytes isolated from POAG patients and exposed to varying concentrations of glucocorticoids has been cited as evidence of a systemic steroid defect in these patients (110–112), but several other laboratories could not confirm these results (113–115). These contrasting results may be explained in part by methodological differences between the studies as well as a potential heterogeneity in responsiveness within the glaucoma population. Further evidence for a lack of increased glucocorticoid sensitivity in glaucoma patients comes from a study reporting no difference in the number of glucocorticoid receptors or glucocorticoid binding affinity between skin fibroblasts isolated from POAG patients and normal controls. In addition, there was no difference in responsiveness of these cells to glucocorticoids as assessed by $^3$H-thymidine incorporation (116).

It has been suggested that POAG is due to an ocular and/or systemic defect in cortisol metabolism (117,118,120). The major route of cortisol metabolism is shown in Fig. 2. Southren et al. reported that trabecular meshwork cells obtained from POAG patients selectively generate the cortisol metabolite 5-dihydrocortisol (DHF), in contrast to TM cells from normals, which do not significantly metabolize cortisol. This production of DHF is due to increased steroid $\Delta^4$-reductase activity and decreased 3-hydroxysteroid dehydrogenase activity (117,118). However, a recent review has questioned the proper verification of these cells as authentic TM cells and the apparent reliance of this hypothesis on cells obtained from a single glaucoma patient (119). Additional work has suggested that there may be a systemic defect in cortisol metabolism in POAG. The authors report that peripheral white blood cells from POAG patients have a 2-fold reduction in 3-hydroxysteroid dehydrogenase activ-

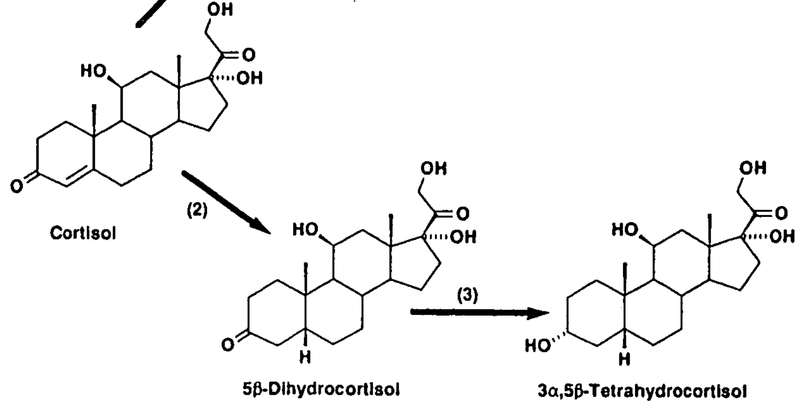


**FIG. 2.** Major pathway for cortisol metabolism. Enzymes: **1**, 5α-$\Delta^4$-reductase; **2**, 5β-$\Delta^4$-reductase; **3**, 3-hydroxysteroid dehydrogenase. Altered cortisol metabolism and the cortisol metabolite dihydrocortisol have been implicated in the pathogenesis of primary open angle glaucoma (see text for details).

ity compared to age-matched control subjects (120). They have proposed that dihydrocortisol (DHF) is involved in the pathogenesis of POAG, and have reported that DHF can potentiate the action of dexamethasone in cultured TM cells (121) and in rabbit IOP studies (122,123). The mechanism of action of DHF is currently unknown. The metabolism of cortisol to DHF eliminates glucocorticoid hormone activity (124), but interestingly, DHF has been shown to have significant mineralocorticoid activity (125). Other investigators have suggested that mineralocorticoids may play a role in the regulation of aqueous humor dynamics (1,2,126). Contrary to this hypothesis, elevated levels of DHF were not found in the aqueous humor of POAG patients (127). Out of all tissues in the eye, it appears that the lens is the most active in metabolizing cortisol (127,128), and aqueous humor levels of DHF may be primarily due to cortisol metabolism by the lens rather than by the TM. We have recently discovered that the lens has the type 1 5α-$\Delta^4$-reductase isoenzyme with relatively high specific activity (Clark AF, Lane D, and Russell DW, 1995, unpublished observations). It should be noted that although most of the reported studies of dihydrocortisol in the TM have used the 5β-isomer of DHF, the predominant isomer found in the aqueous humor and made by the lens is 5α-DHF. However interesting the reported association of cortisol metabolism with POAG, it needs to be independently verified.

To date, there is no clear picture on what role, if any, glucocorticoids play in the pathogenesis of POAG. A number of studies have suggested that glucocorticoids are in many ways associated with POAG, and some of these studies have been independently confirmed in different laboratories. It is possible that glucocorticoids are just one of the many risk factors associated with POAG, or that glucocorticoids may play a role in the pathogenesis of glaucoma in only a subset of POAG patients. The generation of glucocorticoid-induced glaucoma is clearly related to the ocular hypertensive action of these agents. Although ocular hypertension is an important risk factor for the development of POAG, factors other than ocular hypertension may also play an important role in the pathogenesis of this heterogeneous group of diseases. Therefore, glucocorticoid-induced glaucoma may serve as a useful model in which to understand one important aspect of POAG, but it may not necessarily reflect all the different aspects of these diseases.

## EFFECTS OF GLUCOCORTICOIDS ON THE TRABECULAR MESHWORK

Whether or not glucocorticoids are directly involved in the pathogenesis of glaucoma, they do provide a useful model system in which to study the cellular and biochemical mechanisms involved in POAG because they are capable of generating a disease which is in many ways very similar to POAG. As discussed in the previous section, ocular and systemic administration of potent glucocorticoids can generate a progressively elevated intraocular pressure which is due to increased aqueous humor outflow resistance and is associated with specific morphological changes in the trabecular meshwork. Glucocorticoid-induced ocular hypertension can eventually cause secondary open angle glaucoma. A number of investigators have examined the effects of glucocorticoids on the trabecular meshwork in attempt to better understand GIG and primary open angle glaucoma.

An important model system for these studies is cultured human trabecular meshwork cells. Cultured TM cells share many properties with TM cells in situ; both (a) synthesize and secrete very similar extracellular matrix molecules (129–131), (b) have identical cytoskeletal elements including smooth muscle α-actin (132–135), (c) are phagocytic (136,137), (d) express similar extracellular proteinases (138), and (e) have similar junctional complexes (139,140). It is therefore argued that cultured TM cells are an appropriate model for studying many of the biological properties of the TM. The TM, like many tissues, functions as a tissue matrix that involves a dynamic interaction between the extracellular matrix, the TM cell membrane, the cytoskeleton, and the TM cell nucleus. Because of this extensive connectivity, it is not unexpected that glucocorticoids have been shown to influence all of these components of the TM.

TM cells are expected to be targets for glucocorticoid action since they contain intracellular glucocorticoid receptors (3,4). The treatment of cultured human TM cells with glucocorticoids has been shown to (a) alter gene expression (119,141,142), (b) reorganize the TM cytoskeleton (132,143), (c) increase the deposition of certain TM extracellular matrix components (130,144,145), (d) inhibit extracellular proteinase activities (146,147), (e) induce the expression of specific TM proteins (119,142, 148,149), (f) inhibit TM cell phagocytosis (119,142), proliferation (132,142), and migration (132), and (g)

alter TM cell morphology (132,143). Any one of these activities, or combination of these activities, may be responsible for the generation of glucocorticoid-induced glaucoma.

Based on these data, we would like to propose the following hypothesis for the development of glucocorticoid-induced ocular hypertension and glaucoma (Fig. 3): Glucocorticoids (either endogenously generated or exogenously applied) enter the TM cells and activate the glucocorticoid receptor which alters the expression of specific TM cell genes. This altered gene expression causes changes in the TM cytoskeleton, extracellular matrix, membrane junctional proteins, and perhaps also cell adhesion molecules. Several important TM cell functions are inhibited which subsequently leads to increased aqueous humor outflow resistance and the development of ocular hypertension. The elevated IOP can eventually damage the optic nerve head and retinal ganglion cells in certain individuals which results in the characteristic glaucomatous visual field loss. Although this may appear to be an attractive hypothesis, one must remember that it is based in large part on studies that have been conducted with TM cells grown in culture. Care should be taken when extrapolating morphological and biochemical changes reported in cultured TM cells to changes in the outflow facility and TM in situ. There has been much less work studying the effects of glucocorticoids on TM cells in situ.

TM Cells + Glucocorticoids

↓

Altered TM Cell Gene Expression

↓

Biochemical Changes in TM (ECM, Cytoskeleton, Etc.)

↓

Altered TM Cell Function(s)

↓

Increased Aqueous Outflow Resistance

↓

Elevated IOP

↓

Damage to ONH & Retinal Ganglion Cells

↓

Glaucomatous Visual Field Changes

**FIG. 3.** Hypothesis for glucocorticoid-induced ocular hypertension and glaucoma.

There are certain limitations to studying the effects of glucocorticoids on cultured TM cells. There are many aspects of the morphology and biochemistry of TM cells cultured as a monolayer on culture dishes, coverslips, or membranes that are similar to TM cells in situ. However, the TM is a reticulated network of cells and extracellular matrix which cannot be mimicked in cell culture, and it is important to determine whether specific glucocorticoid-mediated effects on the TM are directly associated with increased outflow resistance and elevated IOP. Using an isolated perfusion culture system (144), we have shown that perfusion with DEX ($10^{-7}$ M) for 10–14 days was able to cause an average pressure rise of 17 mm Hg corresponding to a 50% reduction in outflow facility in ~30% of the treated eyes compared to their contralateral untreated eyes (150). The degree of DEX responsiveness in the perfusion cultured human eyes is remarkably similar to that seen in clinical studies. The DEX-induced ocular hypertensive perfused eyes developed many morphological changes in the TM which were very similar to those reported in patients with GIG (77–80), and at least some of the glucocorticoid-induced changes seen in cultured TM cells also occur in DEX perfused ocular hypertensive eyes. This supplies further evidence for the usefulness of these culture systems for the study of the pathogenesis of impaired aqueous outflow and ocular hypertension.

## STEROIDS WHICH LOWER IOP

In contrast to glucocorticoids, which have the propensity to cause ocular hypertension, a variety of steroids have been reported to lower IOP, offering hope that some of these compounds may be useful antiglaucoma agents. Agonists or antagonists from every class of steroid hormone have been reported to lower IOP, including estrogens, androgens, progestins, mineralocorticoids, and glucocorticoids (Fig. 4).

Estrogens and progestins have been suggested to play a role in cyclic variations in IOP during the menstrual cycle and during pregnancy in females (151,152), although not all evidence supports this contention. A detailed and careful analysis failed to correlate changes in endogenous serum progesterone with aqueous humor dynamics during the men-

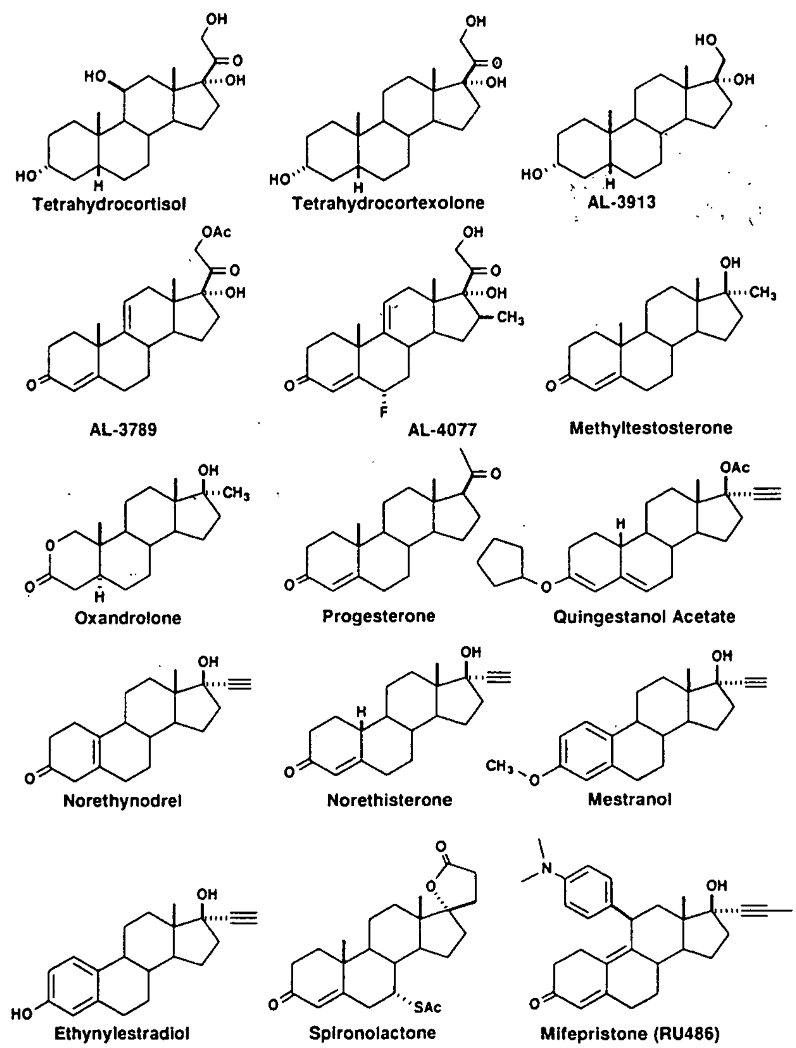


**FIG. 4.** Structures of steroids reported to lower IOP in humans and/or animals.

strual cycle (153). However, the systemic administration of exogenous progesterone has been reported to rapidly (within hours) lower IOP in glaucoma patients (154,155). The topical ocular administration of the progestins progesterone, quingestanol acetate, or norethisterone appear to individually be able to lower IOP in rabbits and primates (156). The mechanism(s) responsible for the progestin-induced IOP-lowering activity is currently not clear as it has been reported to increase outflow in humans (155) and suppress aqueous formation in rabbits (156). Oral administration of the estrogen mestranol (0.1 mg/day) alone, or in combination with the progestin ethynodiol diacetate, for several months gradually lowered intraocular pressure and increased the aqueous humor outflow facility in normal volunteers (157). The combination of mestranol and norethynodrel was also reported to significantly lower IOP in POAG patients already on maximum therapy (158).

Ocular administration of the anabolic androgens methyltestosterone and oxandrolone has been reported to lower DEX-induced ocular hypertension in rabbits (159) and primates (160). In addition, methyltestosterone has been shown to normalize DEX-induced altered glycosaminoglycan profiles in the TM of these animals. It is therefore hypothesized that these androgens lower IOP by increasing aqueous outflow. The finding that it generally takes 1–2 weeks of ocular androgen treatment for the ocular hypotensive effect also supports this contention.

Mineralocorticoids have been reported to play a role in the regulation of aqueous humor production (1,2,126), possibly by controlling the rate of aqueous formation. Receptors for mineralocorticoids

have been identified in the ciliary body (1,2), and the topical administration of the natural mineralocorticoid aldosterone appears to induce ocular hypertension in rabbits (126). The topical ocular administration of the mineralocorticoid antagonist spironolactone has been reported to alter aqueous humor electrolytes (161) and lower IOP in rabbits (126). The ocular hypotensive activity of mineralocorticoid antagonists was also demonstrated in glaucoma patients treated for several weeks with 200 mg spironolactone/day (162).

Because glucocorticoids can alter IOP by increasing aqueous humor outflow resistance, it may be possible to lower IOP through the use of a glucocorticoid antagonist. Mifepristone (RU486) is a potent antiprogestin (163) that also has significant glucocorticoid antagonist activity (163,164). Mifepristone was designed as a progestin receptor antagonist with nanomolar receptor binding affinity, and has been shown to be a potent glucocorticoid receptor antagonist. RU486 was shown to competitively displace dexamethasone from the glucocorticoid receptor of the rabbit iris-ciliary body (165,166). Several reports have shown that topical ocular or subconjunctival administration of RU486 can lower the IOP of normal rabbits (167,168), although this 1–2 mm Hg IOP-lowering appears to be only marginally significant. The topical ocular administration of RU486 appears to partially block glucocorticoid-induced ocular hypertension in rabbits (166,169). An analog of RU486 designed for improved ocular bioavailability had no apparent effect on IOP of rabbits (170), although the authors did not demonstrate that this analog did, in fact, enter the eye. Several other IOP-lowering steroids (progesterone and methyltestosterone) have weak glucocorticoid antagonist activity, and this may be partially responsible for their IOP-lowering activity.

Topical ocular administration of tetrahydrocortisol (THF), a natural metabolite of cortisol, has been reported to lower IOP in DEX-induced ocular hypertensive rabbits but does not alter the IOP of normotensive rabbits (171). THF is devoid of glucocorticoid agonist or antagonist activity (172; Clark AF, Lane D, Wilson K, et al., 1995, unpublished observations). It lacks classical glucocorticoid in vivo and in vitro activities (i.e., antiinflammatory, loss in body weight, induction of systemic hypertension, etc.), nor does it antagonize these DEX-induced effects. In addition, it is not a glucocorticoid receptor antagonist because it has no affinity for the human glucocorticoid receptor (172). Even though THF is not a glucocorticoid antagonist in the classical sense, it has been shown to inhibit DEX-induced cytoskeletal changes in cultured human TM cells in a time and dose-dependent manner (172,173). DEX-induced alterations in the TM cytoskeleton have been proposed to be involved in the generation of ocular hypertension (132,143). THF alone appears to alter the TM cytoskeleton (172,173) as well as regulate TM cell gene expression (149) independent of the glucocorticoid receptor. THF can modify the expression of certain TM proteins which are also regulated by glucocorticoids (149). A preliminary study has suggested that the topical ocular administration of 1% THF qid for 2–6 weeks lowered IOP in eight out of nine POAG patients (174). A larger double masked clinical trial is required to further evaluate the utility of THF as an antiglaucoma agent.

The steroids reported to lower IOP belong to diverse steroid classes. Do they all work through separate mechanisms, or do they work via a common mechanism? Two metabolites of cortisol, tetrahydrocortisol (THF) and tetrahydrocortexolone (THS), were originally thought to be biologically inactive. However, recent studies have demonstrated that THF is capable of lowering IOP in ocular hypertensive eyes (171,174), and THS has angiostatic activity with the ability to inhibit the growth of new blood vessels (175). It now appears that there is a correlation between the IOP-lowering activity and angiostatic activity of certain steroids (159). Angiostatic steroids such as THF, THS, AL-3913, AL-3798, and AL-4077 have been shown to lower IOP in DEX-induced ocular hypertensive rabbits. In addition, steroids with IOP-lowering activity such as methyltestosterone, oxandrolone, and ethynylestradiol have been shown to have angiostatic activity in the chicken embryo chorioallantoic membrane (CAM) model of neovascularization (159). Therefore, there is a correlation of two apparently different activities among steroids of diverse structure. The IOP-lowering action of all these steroids generally requires at least 1–2 weeks of treatment, and indirect evidence suggests that the mechanism of action is at the aqueous outflow facility. Current efforts are focused at determining both the IOP-lowering and angiostatic molecular mechanism(s) of action of these agents. The potential use of these agents for the treatment of glaucoma awaits further testing.

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## REFERENCES

1. Starka L, Obenberger J. Steroids and intraocular pressure. *J Steroid Biochem* 1976;7:979–83.
2. Starka L, Hampl R, Gregorova I, Obenberger J. Aldosterone: its occurrence, metabolism and binding in the rabbit eye. *Exp Eye Res* 1977;25:91–8.
3. Weinreb RN, Bloom E, Baxter JD, et al. Detection of glucocorticoid receptors in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 1981;21:403–7.
4. Hernandez MR, Wenk EJ, Weinstein BI, et al. Glucocorticoid target cells in human outflow pathway: autopsy and surgical specimens. *Invest Ophthalmol Vis Sci* 1983;24:1612–6.
5. Chader GJ, Meltzer R, Silver J. A soluble receptor for corticoids in the neural retina of the chick embryo. *Biochem Biophys Res Commun* 1972;46:2026–33.
6. Weinstein BI, Altman K, Gordon GG, Dunn M, Southren AL. Specific glucocorticoid receptor in the iris-ciliary body of the rabbit. *Invest Ophthalmol Vis Sci* 1977;16:973–6.
7. Wenk EJ, Hernandez MR, Weinstein BI, Gordon GG, Dunn MW, Southren AL. Glucocorticoid receptor binding in bovine lens. *Invest Ophthalmol Vis Sci* 1982;22:599–605.
8. Schleimer RP, Claman HN, Oronsky A. *Anti-inflammatory steroid action: basic and clinical aspects*. San Diego: Academic Press, 1989.
9. Polansky JR, Weinreb RN. Anti-inflammatory agents: steroids as anti-inflammatory agents. In: Sears ML, ed. *Handbook of experimental pharmacology, vol. 69*. Berlin: Springer-Verlag, 1984:459–538.
10. Jaanus SD. Anti-inflammatory drugs. In: Bartlett JD, Jaanus SD, eds. *Clinical ocular pharmacology*. Boston: Butterworths, 1989:163–77.
11. Stern JJ. Acute glaucoma during cortisone therapy. *Am J Ophthalmol* 1953;36:389.
12. Francois J. Cortisone et tension oculaire. *Ann Oculist* 1954;187:805–16.
13. Covall LL. Glaucoma induced by systemic steroid therapy. *Am J Ophthalmol* 1958;45:108–9.
14. Laval J, Collier R. Elevation of intraocular pressure due to hormonal steroid therapy in uveitis. *Am J Ophthalmol* 1955;39:175–82.
15. Bernstein HN, Schwartz B. Effects of long-term systemic steroids on ocular pressure and tonographic values. *Arch Ophthalmol* 1962;68:742–53.
16. Becker B, Mills DW. Corticosteroids and intraocular pressure. *Arch Ophthalmol* 1963;70:500–7.
17. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. *Arch Ophthalmol* 1963;70:482–91.
18. Armaly MF. Corticosteroid glaucoma. In: Cairnes JE, ed. *Glaucoma*. London: Grune and Stratton, 1986:697–710.
19. Kass MA, Johnson T. Corticosteroid-induced glaucoma. In: Ritch R, Shields MB, Krupin T, eds. *The glaucomas*. St. Louis: C. V. Mosby, 1989:1161–8.
20. Skuta GL, Morgan RK. Corticosteroid-induced glaucoma. In: Ritch R, Shields MB, Krupin T, eds. *The glaucomas*. St. Louis: C. V. Mosby (in press).
21. Polansky JR. Side effects of topical ophthalmic therapy with anti-inflammatory steroids and β-blockers. *Curr Opinion Ophthalmol* 1992;3:259–72.
22. Urban RC, Dreyer EB. Corticosteroid-induced glaucoma. *Int Ophthalmol Clin* 1993;33:135–9.
23. Hench PS. The reversibility of certain rheumatic and nonrheumatic conditions by the use of cortisone or of the pituitary adrenocorticotrophic hormone. *Ann Intern Med* 1952;36:1–34.
24. Woods AC. Clinical and experimental observation on the use of ACTH and cortisone in ocular inflammatory disease. *Am J Ophthalmol* 1950;46:1325–49.
25. Gordon DM. Prednisone and prednisolone in ocular disease. *Am J Ophthalmol* 1956;41:593–600.
26. Miller D, Peczon JD, Whitworth CG. Corticosteroids and functions in the anterior segment of the eye. *Am J Ophthalmol* 1965;59:31–4.
27. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. *Invest Ophthalmol* 1965;4:187–97.
28. Becker B. Intraocular pressure response to topical corticosteroids. *Invest Ophthalmol* 1965;4:198–205.
29. Hovland KR, Ellis PP. Ocular changes in renal transplant patients. *Am J Ophthalmol* 1967;63:283–9.
30. Armaly MF. The heritable nature of dexamethasone-induced ocular hypertension. *Arch Ophthalmol* 1966;75:32–5.
31. Schwartz JT, Reuling FH, Feinleib M, Garrison RJ, Collie DJ. Twin study on ocular pressure following topically applied dexamethasone. *Arch Ophthalmol* 1973;90:281–6.
32. Palmberg PF, Mandell A, Wilensky JT, Podos SM, Becker B. The reproducibility of the intraocular pressure response to dexamethasone. *Am J Ophthalmol* 1975;80:844–56.
33. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. II. The effect of dexamethasone in the glaucomatous eye. *Arch Ophthalmol* 1963;70:492–9.
34. Becker B, Hahn KA. Topical corticosteroids and heredity in primary open angle glaucoma. *Am J Ophthalmol* 1964;57:543–51.
35. Francois J, Heitz-De Bree C, Tripathi RC. The cortisone test and the heredity of open angle glaucoma. *Am J Ophthalmol* 1966;62:844–52.
36. Wilensky JT, Snyder D, Gieser D. Steroid-induced ocular hypertension in patients with flittering blebs. *Ophthalmology* 1980;87:240–4.
37. Mermoud A, Salmon JF. Corticosteroid-induced ocular hypertension in draining Molteno single-plate implants. *J Glaucoma* 1993;2:32–6.
38. Becker B, Chevrette L. Topical corticosteroid testing in glaucoma siblings. *Arch Ophthalmol* 1966;76:484–7.
39. Paterson G. Studies of the response to topical dexamethasone of glaucoma relatives. *Trans Ophthalmol Soc UK* 1966;85:295–305.
40. Davies TG. Tonographic survey of the close relatives of patients with chronic simple glaucoma. *Br J Ophthalmol* 1968;52:32–9.
41. Bartlett JD, Woolley TW, Adams CM. Identification of high ocular pressure responders to topical ophthalmic corticosteroids. *J Ocular Pharm* 1993;9:35–45.
42. Becker B. Diabetes mellitus and primary open angle glaucoma: the XXVII Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1971;77:1–16.
43. Podos SM, Becker B, Morton WR. High myopia and primary open-angle glaucoma. *Am J Ophthalmol* 1966;62:1039–43.
44. Gaston H, Absolon MJ, Thurtle OA, Sattar MA. Steroid responsiveness in connective tissue diseases. *Br J Ophthalmol* 1983;67:487–90.
45. Biedner BZ, David R, Grudsky A, Sachs U. Intraocular

pressure response to corticosteroids in children. *Br J Ophthalmol* 1980;64:430–1.
46. Ohji M, Kinoshita S, Ohmi E, Kuwayama Y. Marked intraocular pressure response to instillation of corticosteroids in children. *Am J Ophthalmol* 1991;112:450–4.
47. Podos SM, Krupin T, Asseff C, Becker B. Topically administered corticosteroid preparations. *Arch Ophthalmol* 1971;86:251–4.
48. Kitazawa Y. Increased intraocular pressure induced by corticosteroids. *Am J Ophthalmol* 1976;82:492–5.
49. Cantrill HL, Palmberg PF, Zink HA, Waltman SR, Podos SM, Becker B. Comparison of in vitro potency of corticosteroids with ability to raise intraocular pressure. *Am J Ophthalmol* 1975;79:1012–7.
50. Mindel JS, Tavitian HO, Smith H, Walker EC. Comparative ocular pressure elevation by medrysone, fluorometholone, and dexamethasone phosphate. *Arch Ophthalmol* 1980;98:1577–8.
51. Leibowitz HM, Kupferman A, Stewart RH, Kimbrough RL. Evaluation of dexamethasone acetate as a topical ophthalmic formulation. *Am J Ophthalmol* 1978;86:418–23.
52. Fairbairn WD, Thorson JC. Fluorometholone: anti-inflammatory and intraocular pressure effects. *Arch Ophthalmol* 1971;86:138–41.
53. Eilon LA, Walker SR. Clinical evaluation of clobetasone butyrate eye drops in the treatment of anterior uveitis and its effect on intraocular pressure. *Br J Ophthalmol* 1981;65:644–7.
54. Stewart RH, Smith JP, Rosenthal AL. Ocular pressure response to fluorometholone acetate and dexamethasone sodium phosphate. *Curr Eye Res* 1984;3:835–9.
55. Kupferman A, Leibowitz HM. Anti-inflammatory effectiveness of topically administered corticosteroids in the cornea without epithelium. *Invest Ophthalmol* 1975;14:252–5.
56. Bartlett JD, Horwitz B, Laibovitz R, Howes JF. Intraocular pressure response to loteprednol etabonate in known steroid responders. *J Ocular Pharm* 1993;9:157–65.
57. Ramsell TG, Bartholomew RS, Walker SR. Clinical evaluation of clobetasone butyrate: a comparative study of its effects in postoperative inflammation and on intraocular pressure. *Br J Ophthalmol* 1980;64:43–5.
58. Leibowitz HM, Ryan WJ, Kupferman A. Comparative anti-inflammatory efficacy of topical corticosteroids with low glaucoma-inducing potential. *Arch Ophthalmol* 1992;110:118–20.
59. McGhee CNJ, Watson DG, Midgley JM, Noble MJ, Dutton GN, Fern AI. Penetration of synthetic corticosteroids into human aqueous humor. *Eye* 1990;4:526–30.
60. Spaeth GL. Hydroxymethylprogesterone: an anti-inflammatory steroid without apparent effect on intraocular pressure. *Arch Ophthalmol* 1966;75:783–7.
61. Druzgala P, Wu W-M, Bodor N. Ocular absorption and distribution of loteprednol etabonate, a soft steroid, in rabbit eyes. *Curr Eye Res* 1991;10:933–7.
62. Leibowitz HM, Hyndiuk RA, Lindsey C, Rosenthal AL. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. *Ann Ophthalmol* 1984;16:1110–5.
63. Foster CS, Drake M, Turner FD, et al. Efficacy and safety of 1% Rimexolone opthalmic suspension vs 1% prednisolone acetate (Pred Forte) for treatment of uveitis. In: Nussenblatt RB, Whitcup SM, Caspi RR, Gery I, eds. *Advances in ocular immunology*. Elsevier: Amsterdam, 1994:411–5.
64. Spaeth GL, Rodrigues MM, Weinreb S. Steroid-induced glaucoma: A. Persistent elevation of intraocular pressure. B. Histopathological aspects. *Tr Am Opthalmol Soc* 1977;75:353–81.
65. Espildora J, Vicuna P, Diaz E. Cortisone-induced glaucoma: a report of 44 affected eyes. *J Fr Ophthalmol* 1981;4:503–8.
66. Sugar HS. Low tension glaucoma: a practical approach. *Ann Ophthalmol* 1979;11:1155–71.
67. Kass MA, Kolker AE, Becker B. Chronic topical corticosteroid use simulating congenital glaucoma. *J Pediatr* 1972;81:1175–7.
68. Zugerman C, Sauders D, Levit F. Glaucoma from topically applied creams. *Arch Dermatol* 1976;112:1325–6.
69. Brubaker RF, Halpin JA. Open-angle glaucoma associated with topical administration of flurandrenolide to the eye. *Mayo Clin Proc* 1975;50:322–6.
70. Kalina RE. Increased intraocular pressure following subconjunctival corticosteroid administration. *Arch Ophthalmol* 1969;81:788–90.
71. Herschler J. Increased intraocular pressure induced by repository corticosteroids. *Am J Ophthalmol* 1976;82:90–3.
72. Dreyer EB. Inhaled steroid use and glaucoma. *N Engl J Med* 1993;329:1822.
73. Opatowsky I, Feldman RM, Gross R, Feldman ST. Intraocular pressure elevation associated with inhalation and nasal corticosteroids. *Ophthalmology* 1993;102:177–9.
74. Godel V, Feiler-Ofry V, Stein R. Systemic steroids and ocular fluid dynamics. II. Systemic versus topical steroids. *Acta Ophthalmol* 1972;50:664–76.
75. Haas JS, Nootens RH. Glaucoma secondary to benign adrenal ademonia. *Am J Ophthalmol* 1974;78:497–500.
76. Sayegh F, Weigelin E. Intraocular pressure in Cushing's syndrome. *Ophthalmic Res* 1975;7:390–4.
77. Rohen JW, Linner E, Witmer R. Electron microscopic studies on the trabecular meshwork in two cases of corticosteroid-glaucoma. *Exp Eye Res* 1973;17:19–31.
78. Roll P, Benedikt O. Electronmicroscopic investigation of the trabecular meshwork in cortisonglaucoma. *Klin Mbl Augenheilk* 1979;174:421–8.
79. Toriyama K. An electron microscopic study on the trabecular meshwork in corticosteroid-glaucoma. *Folia Ophthalmol Jpn* 1979;30:1583–9.
80. Rohen JW, Lutjen-Drecoll E. Morphology of aqueous humor outflow pathways in normal and glaucomatous eyes. In: Ritch R, Shields MB, Krupin T, eds. *The glaucomas*. St. Louis: C. V. Mosby, 1989:41–74.
81. Boyd TAS, McLeod LE. Circadian rhythms of plasma corticoid levels, intraocular pressure and aqueous outflow facility in normal and glaucomatous eyes. *Ann NY Acad Sci* 1964;117:597–613.
82. Weitzman ED, Henkind P, Leitman M, Hellman L. Correlative 24-hour relationships between intraocular pressure and plasma cortisol in normal subjects and patients with glaucoma. *Br J Ophthalmol* 1975;59:566–72.
83. Sheridan PT, Brubaker RF, Larrson L-I, Rettig EVS, Young WF. The effect of oral dexamethasone on the circadian rhythm of aqueous humor flow in humans. *Invest Ophthalmol Vis Sci* 1994;35:1150–6.
84. Weinreb RN, Polansky JR, Kramer SG, Baxter JD. Acute effects of dexamethasone on intraocular pressure in glaucoma. *Invest Ophthalmol Vis Sci* 1985;26:170–5.
85. Lorenzetti OJ. Effects of corticosteroids on ocular dynamics in rabbits. *J Pharmacol Exp Ther* 1970;175:763–72.
86. Levine RZ, Rothberger M, Rosenberg S. Corticosteroid glaucoma in the rabbit. *Am J Ophthalmol* 1974;78:505–10.
87. Ticho U, Lahav M, Berkowitz S, Yofee P. Ocular changes in rabbits with corticosteroid-induced ocular hypertension. *Br J Opthalmol* 1979;63:646–50.
88. Francois J, Benozzi G, Victoria-Troncoso V, Bohyn W, Ultrastructural and morphometric study of corticosteroid glaucoma in rabbits. *Ophthalmic Res* 1984;16:168–78.
89. Knepper PA, Breen M, Weinstein HG, Blacik LJ. Intraoc-

ular pressure and glycosaminoglycan distribution in the rabbit eye: effect of age and dexamethasone. *Exp Eye Res* 1978;27:567–75.

90. Knepper PA, Collins JA, Frederick R. Effect of dexamethasone, progesterone, and testosterone on IOP and GAGs in the rabbit eye. *Invest Ophthalmol Vis Sci* 1985;26:1093–100.
91. Bodor N, Bodor N, Wu W-M. A comparison of intraocular pressure elevating activity of loteprednol etabonate and dexamethasone in rabbits. *Curr Eye Res* 1992;11:525–30.
92. Zhan G-L, Miranda OC, Bito LZ. Steroid glaucoma: corticosteroid-induced ocular hypertension in cats. *Exp Eye Res* 1992;54:211–8.
93. Palkama A, Alaranta S, Oksala O, Krootila K, Virtanen I, Uusitalo H. Glucocorticoid induced glaucoma in the cat eye [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1994;35:2774.
94. Keates EU, Druzgala PD, Howes JF, Reaves TA. Loteprednol etabonate: a new steroid without ocular hypertensive effect [ARVO Abstract]. *Invest Opthalmol Vis Sci* 1991;32:1372.
95. Armaly MF. Aqueous outflow facility in monkeys and the effect of topical corticoids. *Invest Ophthalmol* 1964;3:534–8.
96. DeSantis L, Garthwaite C, Knepper PA. Dexamethasone-induction of ocular hypertension in the primate [AFVD Abstract]. *Invest Ophthalmol Vis Sci* 1990;31:488.
97. Kitazawa Y, Horie T. The prognosis of corticosteroid-responsive individuals. *Arch Ophthalmol* 1981;99:819–23.
98. Lewis JM, Priddy T, Judd J, et al. Intraocular pressure response to topical dexamethasone as a predictor for the development of primary open-angle glaucoma. *Am J Ophthalmol* 1988;106:607–12.
99. Ray S, Mehra KS, Misra S, Singh R. Plasma cortisol in glaucoma. *Ann Ophthalmol* 1977;9:1151–4.
100. Rozsival P, Hampl R, Obenberger J, Starka L, Rehak S. Aqueous humor and plasma cortisol levels in glaucoma and cataract patients. *Curr Eye Res* 1981;1:391–6.
101. Schwartz B, McCarty G, Rosner B. Increased plasma free cortisol in ocular hypertension and open angle glaucoma. *Arch Ophthalmol* 1987;105:1060–5.
102. Meredig WE, Pulhorn G, Jentzen F, Hartmann F. The plasmacortisol-level in patients suffering from glaucoma. *Graefes Arch klin Exp Ophthalmol* 1980;213:215–8.
103. McCarty GR, Schwartz B. Increased plasma noncortisol glucocorticoid activity in open-angle glaucoma. *Invest Ophthalmol Vis Sci* 1991;32:1600–8.
104. Berne RM, Levy MN. *Physiology*. St. Louis: C. V. Mosby, 1983:1033–59.
105. Tassman IS. The role of stress in ocular disease. *Trans Am Acad Ophthalmol Otolaryngol* 1957;61:179–93.
106. Weinstein P. Nervism in ophthalmology. *Ophthalmologica* 1954;127:164–78.
107. Becker B, Podos SM, Asseff CF, Cooper DG. Plasma cortisol suppression in glaucoma. *Am J Ophthalmol* 1973;75:73–6.
108. Rosenberg S, Levene R. Suppression of plasma cortisol in normal and glaucomatous patients. *Arch Ophthalmol* 1974;92:6–9.
109. Kass MA, Krupin T, Becker B. Plasma cortisol suppression test used to predict the development of primary open-angle glaucoma. *Am J Ophthalmol* 1976;82:496–7.
110. Bigger JF, Palmberg PF, Becker B. Increased cellular sensitivity to glucocorticoids in primary open-angle glaucoma. *Invest Ophthalmol* 1972;11:832–7.
111. Bigger JF, Palmberg PF, Zink HA. In vitro corticosteroid: correlation response with primary open-angle glaucoma and ocular corticosteroid sensitivity. *Am J Ophthalmol* 1975;79:92–7.
112. Foon KA, Yuen K, Ballintine EJ, Rosenstreich DL. Analysis of the systemic corticosteroid sensitivity of patients with primary open-angle glaucoma. *Am J Ophthalmol* 1977;83:167–73.
113. BenEzra D, Ticho U, Sachs U. Lymphocyte sensitivity to glucocorticoids. *Am J Ophthalmol* 1976;82:866–70.
114. Sowell JG, Levene RZ, Bloom J, Bernstein M. Primary open-angle glaucoma and sensitivity to corticosteroids in vitro. *Am J Ophthalmol* 1977;84:715–20.
115. McCarty G, Schwartz B, Miller K. Absence of lymphocyte glucocorticoid hypersensitivity in primary open angle glaucoma. *Arch Ophthalmol* 1981;99:1258–60.
116. Polansky J, Palmberg P Matulich D, et al. Cellular sensitivity to glucocorticoids in patients with POAG. *Invest Ophthalmol Vis Sci* 1985;26:805–9.
117. Southren AL, Gordon GG, Munnangi PR, et al. Altered cortisol metabolism in cells cultured from trabecular meshwork specimens obtained from patients with primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 1983;24:1413–7.
118. Weinstein BI, Munnangi P, Gordon GG, Southren AL. Defects in cortisol-metabolizing enzymes in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 1985;26:890–3.
119. Polansky JR, Alvarado JA. Cellular mechanisms influencing the aqueous humor outflow pathway. In: Albert DM, Jakobiec FA, eds. *Principles and practice of ophthalmology: basic sciences*. Philadelphia: Saunders, 1994:226–51.
120. Weinstein BI, Iyer RB, Binstock JM, et al. Reduced levels of 3 alpha-hydroxysteroid dehydrogenase in peripheral blood lymphocytes from primary open angle glaucoma patients [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1994;35:1479.
121. Southren AL, Hernandez MR, I'Hommedieu D, Gordon GG, Weinstein BI. Potentiation of collagen synthesis in explants of the rabbit eye by 5β-dihydrocortisol. *Invest Ophthalmol Vis Sci* 1986;27:1757–60.
122. Weinstein BI, Gordon GG, Southren AL. Potentiation of glucocorticoid activity by 5β-dihydrocortisol: its role in glaucoma. *Science* 1983;222:172–3.
123. Southren AL, Gordon GG, I'Hommedieu D, Ravikumar S, Dunn, Weinstein BI. 5β-Dihydrocortisol: possible mediator of ocular hypertension in glaucoma. *Invest Ophthalmol Vis Sci* 1985;26:393–5.
124. Haynes RC. Adrenocorticostopic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Goodman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilmans's. The pharmacological basis of therapeutics*. New York: Pergamon Press, 1990:1431–62.
125. Marver D, Edelman IS. Dihydrocortisol: a potential mineralocorticoid. *J Steroid Biochem* 1978;9:1–7.
126. Panigraphy D, Rupnick MA, Melby JC, Adamis AP. Modulation of intraocular pressure by aldosterone and spironolactone [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1994;35:623.
127. Weinstein BI, Kandalaft N, Ritch R, et al. 5α-Dihydrocortisol in human aqueous humor and metabolism of cortisol by human lenses in vitro. *Invest Ophthalmol Vis Sci* 1991;32:2130–5.
128. Lane D, Clark A. Cortisol metabolism by the lens [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1990;31:825.
129. Hernandez MR, Weinstein BI, Schwartz J, Ritch R, Gordon GG, Southren AL. Human trabecular meshwork cells in culture: morphological and extracellular matrix components. *Invest Ophthalmol Vis Sci* 1987;28:1655–60.
130. Yun AJ, Murphy CG, Polansky JR, Newsome DA, Alvarado JA. Proteins secreted by human trabecular meshwork cells: glucocorticoid and other effects. *Invest Ophthalmol Vis Sci* 1989;30:2012–22.
131. Hernandez MR, Neufeld AH. The extracellular matrix of the trabecular meshwork and optic nerve head. In: Ritch R,

Shields MB, Krupin T, eds. *The glaucomas*. St. Louis: C. V. Mosby, 1989:163–78.
132. Clark AF, Wilson K, McCartney MD, Miggans ST, Kunkle M, Howe W. Glucocorticoid-induced formation of cross-linked actin networks in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 1994;35:281–94.
133. Ryder MI, Weinreb RN, Alvarado J, Polansky J. The cytoskeleton of the cultured human trabecular cell: characterization and and drug responses. *Invest Ophthalmol Vis Sci* 1988;29:251–60.
134. Weinreb RN, Ryder MI. In situ localization of cytoskeletal elements in the human trabecular meshwork and cornea. *Invest Ophthalmol Vis Sci* 1990;31:1839–47.
135. Flugel C, Tamm E, Lutjen-Drecoll E, Stefani FH. Age-related loss of α-smooth muscle actin in normal and glaucomatous trabecular meshwork of different age groups. *J Glaucoma* 1992;1:165–73.
136. Barak MH, Weinreb RN, Ryder MI. Quantitative assessment of cynomolgus monkey trabecular meshwork cell phagocytosis and absorption. *Curr Eye Res* 1988;7:445–8.
137. Rohen JW, van der Zyphen E. The phagocytic activity of the trabecular meshwork endothelium. *Graefes Arch Ophthalmol* 1968;175:143–60.
138. Alexander JP, Samples JR, Van Buskirk EM, Acott TS. Expression of matrix metalloproteinsases and inhibitor by human trabecular meshwork. *Invest Ophthalmol Vis Sci* 1991;32:172–80.
139. Raviola G, Raviola E. Paracellular route of aqueous outflow in the trabecular meshwork and canal of Schlemm: a freeze-fracture study of the endothelial junctions in the sclerocorneal angle of the macaque monkey eye. *Invest Ophthalmol Vis Sci* 1981;21:52–72.
140. McCartney MD, Cantu-Crouch D, Miggans ST, Clark AF. Freeze-fracture analysis of cultured human trabecular meshwork cells: effect of dexamethasone [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1993;34:2154.
141. Chen P, Polansky JR, Hartman C, Zhidong M, Nguyen TD. Expression of trabecular meshwork inducible glucocorticoid response (TIGR) peptide in SF9 cells [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1993;34:3364.
142. Polansky JR, Kurtz RM, Fauss DJ, Kim RY, Bloom E. In vitro correlates of glucocorticoid effects on intraocular pressure. In: Krieglstein GK, ed. *Glaucoma update IV*. Berlin: Springer-Verlag, 1991:20–9.
143. Wilson K, McCartney MD, Miggans ST, Clark AF. Dexamethasone induced ultrastructural changes in cultured human trabecular meshwork cells. *Curr Eye Res* 1993;12:783–93.
144. Johnson DH, Bradley JMB, Acott TS. The effect of dexamethasone on glycosaminoglycans of human trabecular meshwork in perfusion organ culture. *Invest Ophthalmol Vis Sci* 1990;31:2568–71.
145. Steely HT, Browder SL, Julian MB, Miggans ST, Wilson KL, Clark AF. The effects of dexamethasone on fibronectin expression in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 1992;33:2242–50.
146. Snyder RW, Stamer WD, Kramer TR, Seftor REB. Corticosteroid treatment and trabecular meshwork proteases in cell and organ culture supernatants. *Exp Eye Res* 1993;57:461–8.
147. Samples JR, Alexander JP, Acott TS. Regulation of the levels of human trabecular matrix metalloproteinases and inhibitor by interleukin-1 and dexamethasone. *Invest Ophthalmol Vis Sci* 1993;34:3386–95.
148. Tripathi BJ, Millard CB, Tripathi RC. Corticosteroids induce a sialated glycoprotein (Cort-GP) in trabecular cells in vitro. *Exp Eye Res* 1990;51:735–7.
149. Kawase K, Steely HT, Clark AF. The effects of dexamethasone and tetrahydrocortisol on protein expression in cultured human trabecular meshwork cells [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1994;35:2734.
150. Clark AF, Wilson K, de Kater AW, Allingham RR, McCartney MD. Dexamethasone-induced ocular hypertension in perfusion cultured human eyes. *Invest Ophthalmol Vis Sci* 1995;36:478–89.
151. Becker B, Friedenwald JS. Clinical aqueous outflow. *Arch Ophthalmol* 1953;50:557–71.
152. Green K, Phillips CI, Cheeks L, Slagle T. Aqueous humor flow rate and intraocular pressure during and after pregnancy. *Ophthalmic Res* 1988;20:353–7.
153. Gharagozloo NZ, Brubaker RF. The correlation between serum progesterone and aqueous dynamics during the menstrual cycle. *Acta Ophthalmol* 1991;69:791–5.
154. Posthumus RG. The use and the possibilities of progesterone in the treatment of glaucoma. *Ophthalmologica* 1952; 124:17–25.
155. Avasthi P, Luthra MC. Effect of sex hormones on intraocular pressure. *Int Surg* 1967;48:350–5.
156. Lamble JW, Lamble AP. Some effects of progestins, oestrogens and androgens on the ocular tension of rabbits and owl monkeys. *Exp Eye Res* 1978;26:599–610.
157. Treister G, Mannor S. Intraocular pressure and outflow facility: effect of estrogen and combined estrogen-progestin treatment in normal human eyes. *Arch Ophthalmol* 1970; 83:311–8.
158. Meyer EJ, Roberts R, Leibowitz HM, McGowan B, Houle RE. Influence of norethynodrel with mestranol on intraocular pressure in glaucoma. *Arch Ophthalmol* 1966;75:771–3.
159. Clark AF, McNatt L, Knepper PA. Angiostatic steroids as a new class of IOP-lowering compounds [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1994;35:1057.
160. Knepper PA, Garthwaite C, Hvizd M, Goosens W, DeSantis L. Effect of 17-alphamethyltestosterone on IOP and GAG profile of dexamethasone-induced ocular hypertension in primates [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1991;32:998.
161. Starka L, Obenberger J, Louzensky G. Effect of Aldactone administration into the rabbit eye. *Ophthalmic Res* 1981; 13:160–4.
162. Witzmann R. The effect of spironolactone on intraocular pressure in glaucoma patients. *Klin Mbl Augenheilk* 1980; 176:445–6.
163. Baulieu E-E. RU-486 as an antiprogesterone steroid: from receptor to contragestion and beyond. *JAMA* 1989;262: 1808–14.
164. Bertagna X, Bertagna C, Luton J-P, Husson J-M, Girard F. The new steroid analog RU486 inhibits glucocorticoid action in man. *J Clin Endocrinol Metab* 1984;59:25–8.
165. Munden PM, Schmidt TJ. Mifepristone blocks specific glucocorticoid receptor binding in rabbit iris-ciliary body. *Arch Ophthalmol* 1992;110:703–5.
166. Denis P, Elena PP, Nordmann JP, Sarrieau A, Saraux H, Rostene W. Mifepristone (RU486): in vitro binding to glucocorticoid receptors in iris-ciliary body and in vivo effects on intraocular pressure in rabbits [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1993;34:1115.
167. Green K, Phillips CI, Gore SM, Elijah RD, Bowmann KA, Cullen P. Ocular fluid dynamics response to topical RU-486, a steroid blocker. *Curr Eye Res* 1985;4:605–12.
168. Tsukahara S, Sasaki T, Phillips CI, Gore SM. Subconjunctival suspension of RU486 lowers intraocular pressure in normal rabbits. *Br J Ophthalmol* 1986;70:451–5.
169. Green K, Cheeks L, Slagle T, Phillips CI. Interaction between progesterone and mifepristone on intraocular pressure in rabbits. *Curr Eye Res* 1989;8:317–20.
170. Phillips CI, Corrie JET, Gore SM. Water-soluble methochloride of RU486 fails to reduce intraocular pressure in normal rabbits. *Ophthalmic Res* 1987;19:61–4.

171. Southren AL, l'Hommedieu D, Gordon GG, Weinstein BI. Intraocular hypotensive effect of topically applied cortisol metabolite: 3α, 5β-tetrahydrocortisol. *Invest Ophthalmol Vis Sci* 1987;28:901–3.
172. Clark AF, Wilson K, Miggans ST, Lane D. Tetrahydrocortisol inhibits dexamethasone induced cytoskeletal reorganization in cultured human trabecular meshwork cells [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1993;34:2151.
173. McCartney MD, Wilson K, Miggans ST, Clark AF. Effect of dexamethasone and tetrahydrocortisol on cultured human trabecular meshwork cell microfilament and microtubule structure [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1994;35:2735.
174. Southren AL, Wandel T, Gordon GG, Weinstein BI. Treatment of glaucoma with 3α, 5β-tetrahydrocortisol: a new therapeutic modality. *J Ocular Pharm* 1994;10:385–91.
175. Crum R, Szabo S, Folkman J. A new class of steroids inhibits angiogenesis in the presence of heparin or a heparin fragment. *Science* 1985;230:1375–8.